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A Randomised Comparison of CPX-351 and FLAG-Ida in Adverse Karyotype AML and High-Risk MDS: The UK NCRI AML19 Trial

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Abstract:
Liposomal daunorubicin and cytarabine (CPX-351) improves overall survival (OS) compared to 7+3 chemotherapy in older patients with secondary acute myeloid leukaemia (AML); to date there have been no randomized studies in younger patients. The high-risk cohort of the UK NCRI AML19 trial (ISRCTN78449203) compared CPX-351 with FLAG-Ida in younger adults with newly-diagnosed adverse cytogenetic AML or high-risk myelodysplastic syndromes (MDS). 189 patients were randomized (median age 56y). By clinical criteria 49% had de novo AML, 20% secondary AML and 30% high risk MDS. MDS-related cytogenetics were present in 73% of patients, with complex karyotype in 49%. TP53 was the most commonly mutated gene, in 43%. Myelodysplasia-related gene mutations were present in 75 patients (44%). The overall response rate (CR + CRi) after course two was 64% and 76% for CPX-351 and FLAG-Ida (OR:0.54, 95%CI 0.28-1.04, p=0.06). There was no difference in OS (13.3 months vs 11.4 months, HR:0.78, 95%CI 0.55-1.12, p=0.17) or event-free survival (HR:0.90, 95%CI 0.64-1.27, p=0.55) in multivariable analyses. However, relapse-free survival was significantly longer with CPX-351 (median 22.1 vs 8.35 months, HR:0.58, 95% CI 0.36-0.95, p=0.03). There was no difference between the treatment arms in patients with clinically defined secondary AML (HR:1.1, 95%CI 0.52-2.30) or those with MDS-related cytogenetic abnormalities (HR:0.94, 95%CI 0.63-1.40), however an exploratory sub-group of patients with MDS-related gene mutations had significantly longer OS with CPX-351 (median 38.4 vs 16.3 months, HR:0.42, 95%CI 0.21-0.84, heterogeneity p=0.05). In conclusion, OS in younger patients with adverse risk AML/MDS was not significantly different between CPX-351 and FLAG-Ida.

Conflict of interest: COI declared - see note

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A randomised comparison of CPX-351 and FLAG-Ida in adverse karyotype AML and high-risk MDS: the UK NCRI AML19 trial

Short title: CPX-351 vs FLAG-Ida in high-risk AML and MDS

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KEY POINTS

1. In high-risk AML and MDS CPX-351 did not improve response or survival compared to FLAG-Ida but produced better relapse-free survival

2. In the exploratory sub-group of patients defined by the presence of mutations in MDS-related genes CPX-351 improved overall survival

Abstract

Liposomal daunorubicin and cytarabine (CPX-351) improves overall survival (OS) compared to 7+3 chemotherapy in older patients with secondary acute myeloid leukaemia (AML); to date there have been no randomized studies in younger patients. The high-risk cohort of the UK NCRI AML19 trial (ISRCTN78449203) compared CPX-351 with FLAG-Ida in younger adults with newly-diagnosed adverse cytogenetic AML or high-risk myelodysplastic syndromes (MDS). 189 patients were randomized (median age 56y). By clinical criteria 49% had *de novo* AML, 20% secondary AML and 30% high risk MDS. MDS-related cytogenetics were present in 73% of patients, with complex karyotype in 49%. *TP53* was the most commonly mutated gene, in 43%. Myelodysplasia-related gene mutations were present in 75 patients (44%). The overall response rate (CR + CRi) after course two was 64% and 76% for CPX-351 and FLAG-Ida (OR:0.54, 95%CI 0.28-1.04, p=0.06). There was no difference in OS (13.3 months vs 11.4 months, HR:0.78, 95%CI 0.55-1.12, p=0.17) or event-free survival (HR:0.90, 95%CI 0.64-1.27, p=0.55) in multivariable analyses. However, relapse-free survival was significantly longer with CPX-351 (median 22.1 vs 8.35 months, HR:0.58, 95% CI 0.36-0.95, p=0.03). There was no difference between the treatment arms in patients with clinically defined secondary AML (HR:1.1, 95%CI 0.52-2.30) or those with MDS-related cytogenetic abnormalities (HR:0.94, 95%CI 0.63-1.40), however an exploratory sub-group of patients with MDS-related gene mutations had significantly longer OS with CPX-351 (median 38.4 vs 16.3 months, HR:0.42, 95%CI 0.21-0.84, heterogeneity p=0.05). In conclusion, OS in younger patients with adverse risk AML/MDS was not significantly different between CPX-351 and FLAG-Ida.

Introduction

The treatment of AML with adverse karyotype remains unsatisfactory. These patients have a lower response rate, a higher risk of refractory disease and a shorter duration of remission in those who do respond[1–4]. Although the only curative treatment is allogeneic stem cell transplant (SCT), better induction strategies are required to increase the proportion of patients reaching SCT. Improved induction treatments could also potentially improve survival after SCT.

For decades the induction strategy for these patients has been standard 7+3 chemotherapy with daunorubicin and cytarabine (DA). More recently, since there is substantial overlap between high-risk cytogenetic abnormalities and those considered to be myelodysplasia-related[5,6], a relatively high proportion of these patients are eligible for treatment with CPX-351 provided the karyotype is known at the time of treatment initiation. CPX-351 is a liposomal formulation of cytarabine and daunorubicin encapsulated at a pre-clinically identified optimally synergistic 5:1 ratio. Following on from a randomised Phase 2 study[7], CPX-351 demonstrated a higher response rate with improved overall survival (OS) compared to 7+3 in patients aged 60-75 years with prior MDS or CMML, therapy related AML, or an MDS-related karyotype (median OS 9.56 vs 5.95 months, P= 0.003)[8,9]. The rate of SCT was higher in the CPX-351 arm compared with the 7 + 3 arm (34% versus 25%), with a landmark survival analysis from the time of SCT also favouring CPX-351 (median OS NR vs 10.25 months; p =0.009). These findings led to the approval of CPX-351 in younger as well as older patients with newly diagnosed secondary AML although it is important to note that there is currently no randomised evidence of benefit in patients aged <60y.

The widespread availability of sequencing technologies has significantly altered AML classification in recent years[5,6,10,11]. Secondary AML has traditionally been a term used to describe patients whose disease evolved from a prior myeloid disorder (MDS, MPN or MDS/MPN) or after exposure to cytotoxic therapy[2,8,10,11]. However a number of studies have demonstrated that mutational status, in particular mutations in *TP53* and 'secondary-like' genes, may better define distinct clinicopathological subgroups[12,13], and these findings have been incorporated into the most recent classification systems. The World Health Organisation (WHO) now defines *AML, myelodysplasia related* as the presence of either a mutation in one of *ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2,*

U2AF1 or *ZRSR2*; an MDS-related cytogenetic abnormality or a prior history of MDS or MDS/MPN[6]. The International Consensus Classification (ICC) and European Leukaemia Net (ELN) further prioritise genomics, with a mutation in the same list of genes or *RUNX1* classifying a patient as *AML or MDS/AML with myelodysplasia-related gene mutations,* while those with MDS-related cytogenetic abnormalities only are described as *AML or MDS/AML with myelodysplasia-related cytogenetic abnormalities*. A clinical history of MDS or MDS/MPN is added only as a diagnostic qualifier[5,14]. Importantly, the potential benefit of CPX-351 in patients with AML/MDS with myelodysplasia-related gene mutations has not previously been analysed.

We previously reported in the UK National Cancer Research Institute (NCRI) AML17 trial that the FLAG-Ida regimen resulted in superior OS compared to daunorubicin and clofarabine when given as post-induction therapy in younger adults with high-risk AML[15]. Furthermore, in an exploratory study of 115 patients entered into the Medical Research Council (MRC) AML15 trial with secondary AML and a median age of 52 years who otherwise fitted the entry criteria for the CPX-351 pivotal trial, survival was improved for patients treated with FLAG-Ida compared to daunorubicin and cytarabine +/- etoposide[16]. This finding was consistent with the favourable effect of FLAG-Ida on relapse seen in AML15 that was apparent in all demographic subgroups, including adverse risk cytogenetics[17]. We therefore considered FLAG-Ida as the standard of care for younger patients with high-risk AML and MDS and the appropriate control arm for a randomised comparison against CPX-351 in the high-risk cohort of the NCRI AML19 trial.

Patients and methods

The UK NCRI AML19 trial (ISRCTN78449203) enrolled younger adults with newly diagnosed AML or MDS with >10% blasts between November 2016 and November 2020. Patients were generally <60y but older patients could enter if deemed fit by the treating physician. Patients were eligible for various randomisations depending on their cytogenetic and molecular characteristics (supplemental Figure 1).

Patients with a known adverse karyotype at diagnosis according to MRC 2010 criteria[18] or who had high-risk MDS with ≥10% blasts were eligible for a high-risk randomisation between CPX-351 and FLAG-Ida. From July 2018 MDS patients with 5%-9% bone marrow blasts and an IPSS-R very high, high or intermediate (providing that the IPSS-R is > 3.5) were made eligible. Patients were randomised 2:1 in favour of CPX-351, stratified by age group, performance status, and clinical disease type (de novo or secondary AML). The final numbers randomised are less than the 2:1 ratio because of CPX-351 supply issues early in the trial.

As well as this group (Group 1, n=189), other patients could also enter the high-risk randomisation at post-induction time points: Group 2 (n=264) were randomised after induction course 1 and were high risk by a validated risk score, had *FLT3*-ITD without an *NPM1* mutation, or had refractory disease; Group 3 (n=178) were randomised after course 2 if they had persisting MRD by flow cytometry or by RT-qPCR for *NPM1* transcripts, or at the time of relapse (supplemental Figure 1). Here we present results for patients in Group 1, with a CONSORT diagram shown in Figure 1.

FLAG-Ida comprised fludarabine 30 mg/m2 i.v. on days 2–6 inclusive, cytarabine 2 g/m2 over 4 h starting 4 hours after fludarabine on days 2–6, G-CSF (lenograstim 263 μg) subcutaneous daily on days 1–7; idarubicin 8 mg/m2 i.v. daily on days 4–6. Up to 2 courses could be given followed by 2 courses of consolidation with MACE then MiDAC chemotherapy[17] if no donor was available. CPX-351 induction course 1 consisted of 100 units/m^2 (100 mg/m^2 cytarabine and 44 mg/m^2 daunorubicin) administered as a 90-minute infusion on days 1, 3, and 5. A second induction course of 100 units/m^2 was administered on days 1 and 3 in all patients. For patients with complete remission (CR) or CR with incomplete blood count recovery (CRi) after induction course 2, post-remission therapy consisted of up to two cycles of 65 units/m^2 CPX-351 (65 mg/m^2 cytarabine and 29 mg/m^2 daunorubicin) on days 1

and 3. Allogeneic SCT was recommended for all patients post-induction if an appropriately matched donor was available. The trial was approved by the Wales Multicentre Research Ethics Committee and each institution's ethical committee in accordance with the Declaration of Helsinki.

Statistical Analyses

Full details of the statistical analyses are given in the Supplemental appendix. The adverse karyotype randomisation was not prospectively powered in the original study design, hence all reported p-values are nominal. Primary analyses are by intention to treat, and the primary endpoint of this randomisation was OS. End points were defined according to the revised International Working Group criteria[19]. OS was defined as time from randomisation to death from any cause with those still alive censored at date last seen. Final data cut-off was on 17 May 2022. Relapse-free survival (RFS) was calculated only for patients who achieved CR and was measured from the date of attaining CR until the date of disease relapse or death from any cause. Event free survival (EFS) was measured in all patients and was defined as time from randomisation to treatment failure (refractory disease or partial response) by end of course 2, disease relapse, or patient death from any cause. For the outcomes of OS, RFS, EFS and CR achievement, multivariable analyses were adjusted by all stratification variables used at the time of randomisation (namely: age group, gender, performance status, baseline white blood cell count and disease type).

Responses were based on investigator assessment of bone marrows. Toxicity (hematologic recovery times and non-hematologic toxicity) was scored using the National Cancer Institute Common Toxicity Criteria, Version 3, and resource use data (blood product support, days on antibiotics, and hospitalization) were collected.

Characteristics of the patients are summarised across the groups using frequency and percentage for categorical data, and median and quartile range for quantitative data. Comparisons of patient characteristics use chi-squared, Mantel-Haenszel tests for trend, or Wilcoxon rank sum tests as appropriate. Time-to-event outcomes were compared using log-rank tests and Cox regression, or Gray's test for cumulative incidence with competing risk analyses. Outcomes are reported as effect sizes with 95% confidence intervals.

Cytogenetic and Genomic Analyses.

Karyotype analyses were carried out in accredited regional laboratories and reports reviewed centrally. Cytogenetic classifications were defined by MRC 2010 criteria[18]. Following the completion of the trial, banked diagnostic DNA was analysed for variants in 41 recurrently mutated myeloid genes (supplemental Table 1), including the entire coding regions of all myelodysplasia-related genes according to 2022 WHO, ICC and ELN criteria (*ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*)[5,6,14]. Libraries were prepared using the Agilent SureSelect XT HS2 platform and sequenced on an Illumina NextSeq2000, achieving a median depth of 955x. Further details are provided in the supplemental appendix.

Results

Patient Population

Between November 2016 and November 2020, 189 patients with AML or high-risk MDS were randomised, of whom 2 later withdrew consent. Their median age was 56y (range 18 to 70y with 51 patients aged >60y). Patient characteristics by randomisation are shown in Table 1. Of the whole cohort, 49% were classified by clinical features as *de novo* AML, 20% as secondary AML and 30% as high-risk MDS. 8% had a history of previous chemotherapy or radiotherapy. Myelodysplasia-related cytogenetic abnormalities were present in 73% of patients, with a complex karyotype in 49%. Next-generation sequencing results were available for 171/187 patients (91%). *TP53* was the most commonly mutated gene, identified in 44% of patients, followed by *DNMT3A* (19%) and *ASXL1* (18%) (Supplemental Figure 2 and supplemental Table 2). A mutation in at least one MDS-related gene was present in 75/171 (44%) patients, of whom 59 (35%) were categorised as AML/MDS with myelodysplasia-related gene mutations, which by ICC 2022 criteria requires the absence of *TP53* variants[5]. Most patients had mutations in more than one MDS-related gene (Table 1). In this cohort 35% of patients who had a clinical diagnosis of *de novo* AML were found to have myelodysplasia-related gene mutations (Supplemental Figure 3).

Induction Response

There was a trend to higher overall response rate (ORR, i.e. CR+CRi) for patients randomised to FLAG-Ida (Table 2). After cycle 1 the ORR was 51% vs 65% for CPX-351 and FLAG-IDA respectively (p=0.15). After cycle 2 the ORR was 64% vs 76% (OR 0.54; 95% CI 0.28-1.04, p=0.06). Day 30 and day 60 mortality were not different between the treatment arms (day 30, 5% vs 7%, p=0.46; day 60, 12% vs 11%, p=0.77 for CPX-351 and FLAG-Ida respectively). 7 patients randomised to CPX-351 received FLAG-Ida as course 2 due to refractory disease, 3 of whom achieved a CRi. The median number of courses administered in both arms was 2, with only one patient in the FLAG-Ida arm proceeding to consolidation, as compared to 19 patients who received at least one consolidation cycle of CPX-351 (Figure 1).

Toxicity

Platelet recovery to >100x10^9/L was longer with CPX-351 in course 1 with median days to platelet recovery of 34 for CPX-351 vs. 29 for FLAG-Ida ($p<0.001$) with no difference in neutrophil recovery to 1.0 x10^9/L (32 days for CPX-351 vs 30 for FLAG-Ida, p=0.11, Table 2). The most important differences were seen after course 2, with significantly fewer patients recovering neutrophils and platelets, and time to recovery markedly delayed in those that did (31 v 46 days for neutrophils, p=0.002, and 31 v 36 days for platelets, p=0.19, Table 2). This resulted in longer hospitalisation in course 2 with FLAG-Ida (27 v 35.5 days, p=0.002), as well as greater requirements for blood transfusion, platelet transfusion and IV antibiotics (supplemental Table 3). Grade 3 or higher non-haematological toxicities with CPX-351 were comparable being present in 18% compared to 21% with FLAG-Ida (supplemental Table 4).

Survival outcomes

OS at 3 years was 32% and 25% and median OS was 13.3 months vs 11.4 months for CPX-351 and FLAG-Ida respectively (HR 0.85, 95%CI 0.6-1.21, p=0.36). EFS was not significantly different (HR 0.97, 95%CI 0.69-1.37, p=0.86) (Figure 2 and Table 2). In patients achieving CR, RFS at 3 years was 39% and 29% and median RFS was 22.1 months vs 8.35 months (HR 0.66, 95% CI 0.41-1.06, p=0.08) for CPX-351 and FLAG-Ida respectively (Figure 2). In a multivariable Cox regression model adjusting for gender, age group, performance status, baseline white blood cell count, disease type, cytogenetic risk, *NPM1* and *FLT3* mutation status, there remained no benefit in OS (HR 0.78, 95%CI 0.55-1.12, p=0.17) and EFS (HR 0.9, 95%CI 0.64-1.27, p=0.55) while RFS was better with CPX-351 (HR 0.58, 95% CI 0.36-0.93, p=0.03). The RFS advantage was predominantly due to a lower cumulative incidence of death in remission in the CPX-351 arm, with the incidence of relapse being similar (Figure 2).

Numerically a greater number of patients receiving CPX-351 were transplanted although this did not reach statistical significance. overall (53/105, 51% vs 36/82, 44% p=0.41) and more patients receiving CPX-351 were transplanted in first remission (43/67, 64%) compared to those receiving FLAG-Ida (30/62, 48%, p=0.10). The median number of courses given prior to SCT was 2 in both

arms and the median time to SCT was 139 days with CPX-351 and 131 days with FLAG-Ida (p=0.86). The cumulative incidence of death in remission censored at SCT was higher with FLAG-Ida (supplemental Figure 4). Amongst patients who were transplanted, survival did not differ according to induction regimen (supplemental Figure 5).

Exploratory subgroup analyses by genomic class

In patients with secondary AML defined by clinical history only, there was no difference in OS between the treatment groups (HR 1.0, 95%CI 0.59 – 1.69). In patients with high-risk MDS there was a trend to longer OS in patients treated with CPX-351 (HR 0.54, 95%CI 0.28 – 1.00) however the p value for heterogeneity was 0.23 for this analysis (Figure 3). When secondary disease was defined by the presence of myelodysplasia-related cytogenetic abnormalities, there was no difference between treatment arms (HR 0.94, 95%CI 0.63 – 1.40) (Figures 3 and 4).

In patients with mutationally defined secondary AML/MDS, those treated with CPX-351 had significantly longer OS, median 38.4 months with CPX-351 and 16.3 months with FLAG-Ida (HR 0.42, 95%CI 0.21 – 0.85, p value for heterogeneity 0.05) (Figure 3 and 4) despite a similar ORR (70% vs 62%, p=0.5) and no decrease in relapse (3-yr CIR 19% vs 20%). Outcomes were similar in patients with mutations in one compared to ≥2 MDS-related genes (supplemental Figure 6). Patients with MDS-related gene mutations had significantly more haematological toxicity in after the second course of FLAG-Ida compared to patients in other genomic groups, whereas this difference was not seen with CPX-351 (supplemental Table 4).

Patients with *TP53* mutations had an adverse prognosis, with median OS of 7 months compared to 28 months in those with wild-type *TP53*. There was no difference between treatment arms for this group (HR 0.89, 95%CI 0.55 – 1.45). *TP53* mutations were present in all clinical groups but were enriched in those with MDS-related cytogenetics (Supplemental Figure 3).

Measurable residual disease

Bone marrow measurable residual disease (MRD) results were available for 59 patients, either flow cytometry after cycle 1 (n=47, CPX-351 31 and FLAG-Ida

16) or RT-qPCR after cycle 2 (n=12, CPX-351 8 and FLAG-Ida 4; comprising 4 *NPM1,* 7 *KMT2A* rearrangements and 1 *PICALM*::*AF10* fusion). Using a cut-off of <0.1% for MFC MRD and >4 log reduction from the diagnostic result for RT-qPCR, 22 of 59 (37%) of patients achieved an MRD response. Patients who achieved an MRD response had longer OS than those who did not (median 24.3m vs 8.4 months). MRD response was higher in the FLAG-Ida patients (11/20, 55%) than those receiving CPX-351 (11/39, 28%), with the same trend seen when MRD was analysed as a continuous variable (supplemental Figure 6). Results were similar when limiting the analysis to those with flow cytometric MRD results (supplemental Tables 6 and 7). In the small subgroup of patients with MDS-related gene mutations, the rate of MRD response was similar in both arms, 4 of 11 (36%) with CPX-351 and 3 of 9 (33%) with FLAG-Ida.

Discussion

Previous UK NCRI trials established the FLAG-Ida regimen as a preferred regimen in patients aged <60y with high-risk and secondary AML[15,16]. CPX-351 is approved for the treatment of adults with newly diagnosed AML with myelodysplasia-related changes (AML-MRC) and therapy-related AML (t-AML), irrespective of age, but based upon a randomised comparison with 7+3 chemotherapy in older patients only[8].

In this randomised comparison between FLAG-Ida and CPX-351 in younger adults with newly diagnosed AML and high-risk MDS with an adverse karyotype, there was no detectable difference in OS between the treatments. Interestingly, despite the trend to a lower overall response rate and a lower proportion achieving MRD negativity with CPX-351, there was a trend to a higher rate of SCT as was observed in the pivotal CPX-351 trial[8]. Patients who were able to reach SCT had good outcomes irrespective of randomisation. In patients who achieved CR, RFS favoured CPX-351, although the numerically lower CR rate with CPX-351, and therefore smaller proportion of patients included in the RFS calculation, should be noted. The RFS advantage may be related to the reduced number of deaths in remission which allowed more patients to reach transplant. Despite this study enrolling a younger population, the higher rate of death in remission in the control arm is consistent with that seen in the registration study[8]. The second course of FLAG-Ida was associated with delayed count recovery and reduced the benefit of a higher response rate suggesting that in responding patients earlier SCT or a less intensive second course as bridging to SCT may have improved outcomes. In this context FLAG-Ida augmented by the addition of Venetoclax has been reported to give high remission rates following a single course that can be successfully consolidated by SCT[20].

In light of the previously demonstrated benefit of CPX-351 in secondary AML we performed an exploratory analysis of patients with a clinical or cytogenetic diagnosis of secondary AML in which there was no advantage for CPX-351. However, a significant survival benefit with CPX-351 over FLAG-Ida was seen in patients with secondary AML as defined by the presence of MDS-related gene mutations, with the important caveat of small numbers and potential unmeasured confounders within this subgroup analysis. We suggest that this benefit was driven by a combination of lower toxicity and a trend towards higher transplant rate, findings which are consistent with those from the Phase 3

randomised trial of CPX-351 versus 3+7 in older patients[8]. It is increasingly recognised that secondary AML may be better defined by mutational profile than clinical history[5,6,13,14], however patients with molecularly defined secondary AML were not specifically studied in previous trials. Our finding of a survival benefit in this category supports the genomic definition of secondary AML. A previous study from our group had suggested a worse outcome for patients with mutations in 2 or more MDS-related genes, an effect not noted in this study where these patients were treated as high risk and recommended for transplant[21]. We observed no benefit in patients with *TP53* mutations, consistent with a secondary analysis of the phase 3 randomised trial of CPX-351[22] and a French real-world study[23], even when these occurred in the presence of secondary AML mutations. Given almost half those with clinically defined secondary AML and almost 60% with MDS-related cytogenetics had *TP53* mutations, the lack of benefit in these groups may be mediated by the co-existence of *TP53* mutations.

Although our observations require validation in other prospective studies, if confirmed these exploratory findings have important implications for the rational use of CPX-351. Consistent with previous reports[21,24–26], we found a significant proportion of patients with a clinical diagnosis of *de novo* AML who had mutations in MDS-related genes and benefited from treatment with CPX-351. Conversely, many patients with a clinical diagnosis of secondary AML do not benefit from this therapy. Therefore, improving outcomes in this group is likely to require rapid availability of NGS results prior to initiation of therapy.

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Authorship contributions

NHR was the chief investigator and designed the study. CWB and JW provided statistical analyses. LMB, JC, ELH, SB provided trial coordination. RD, SK, SDF, UMO, PM, PK, JC, CH, CA, MD and NHR enrolled patients onto the study. AG undertook molecular analyses and coordinated patient samples. Data analysis was undertaken by CWB and JO at the Centre for Trials Research, Cardiff University. RD, NP and NHR were responsible for molecular MRD analyses. SDF performed flow cytometric MRD analyses. JO, RD and WV performed and analysed genomic sequencing. MK was responsible for DNA library preparation and sequencing. JO, CWB, RD and NHR drafted the paper, which was revised and approved by all authors.

Data sharing statement

Access to de-identified data, and supporting documentation, is available via formal application to Cardiff University via the corresponding author:

Nigel.russell@nottingham.ac.uk. Cardiff University is committed to open access to de-identified clinical trial data.

Disclosure of Conflicts of Interest

JO, CWB, LMB, JC, ELH, JW, SB, WV, MK, AG, NP, UMO, PK, JC, CH, CA and MD have no conflicts to declare.

RD declares research funding from Abbvie and Amgen and consultancy with Astellas, Pfizer, Novartis, Jazz, Beigene, Shattuck and AvenCell.

SK declares research funding from Novartis; Speakers Bureau with Astellas, Novartis and Jazz; consultancy with Servier and BMS.

SDF declares research funding from Jazz and BMS; Speakers Bureau with Jazz, Pfizer and Novartis; advisory committee with Neogenomic

PM declares Honoraria and Speakers Bureau from Pfizer, Jazz, Abbvie and Astellas.

NHR declares research funding from Jazz and Pfizer; honoraria from Pfizer, Servier and Astellas.

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Tables

Table 1. Baseline characteristics in each arm

	FLAG-IDA (n=82)	**CPX-351 (n=105)**
Median age, years (range)	55 (18-67)	57 (23-70)
Age group		
<39	14 (17%)	9 (8.6%)
40-49	12 (15%)	16 (15%)
50-59	34 (41%)	51 (48%)
60+	22 (27%)	29 (28%)
Female sex	34 (41%)	45 (43%)
Diagnosis		
De Novo AML	42 (51%)	50 (48%)
Secondary AML	17 (21%)	21 (20%)
High Risk MDS	23 (28%)	34 (32%)
Prior history		
History of prior cytotoxic / radiotherapy	9 (11%)	7 (6.8%)
History of MDS/MPN	17 (21%)	16 (16%)
WHO performance status		
0 (Normal activity)	48 (59%)	52 (49%)
1 (Restricted activity)	29 (35%)	46 (44%)
2 (In bed <50% waking hours)	5 (6%)	7 (7%)
Cytogenetics + FISH[#]		
Complex ≥3 abnormalities	43 (54%)	51 (50%)
Complex ≥4 abnormalities	40 (51%)	49 (48%)
-5 / del5q / add5q	32 (40%)	45 (43%)
-7 / del7q / add7q	36 (45%)	46 (44%)
-17 / abn17p	12 (15%)	25 (24%)
11q23	6 (8%)	8 (7.7%)
3q21	3 (4%)	6 (5.8%)
MDS-related cytogenetics (WHO 2016)	60 (75%)	74 (71%)
Cytogenetic risk group (MRC 2010)		
Adverse	69 (84%)	87 (83%)
Intermediate	11 (13%)	17 (16%)
Missing/failed	2 (2%)	1 (1.0%)
Mutations		
TP53*	32 (43%)	43 (45%)
Mutation in MDS-related gene*^	38 (51%)	37 (29%)
AML/MDS with MDS-related gene mutation (without co-mutation in *TP53*)*^	29 (39%)	30 (31%)
1 mutated MDS-related gene*^	10 (14%)	8 (8%)
≥2 mutated MDS-related genes*^	19 (26%)	22 (23%)

NPM1 mutant	2 (2%)	4 (4%)
FLT3 TKD	1 (1%)	1 (1%)
FLT3 ITD	4 (5%)	4 (4%)
ELN 2022 risk group		
Adverse	78 (95%)	99 (94%)
Intermediate	3 (4%)	5 (5%)
Missing	1 (1%)	1 (1%)

[#]Missing in 3 patients

*Percentages of those with gDNA for sequencing (171 of 187 patients)

^*ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*

AML, acute myeloid leukaemia; ELN, European Leukaemia Net; FISH, fluorescence in situ hybridisation; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; MRC, Medical Research Council; WHO, World Health Organisation.

Table 2. Response and outcomes in each group (FLAG IDA / CPX)

	FLAG-IDA (n=82)	**CPX-351 (n=105)**	**p value**
Response after cycle 1			
CR	42 (51%)	42 (40%)	0.15
CRi	11 (13%)	12 (11%)	
ORR (CR+CRi)	53 (65%)	54 (51%)	
Best response after 2 cycles			
CR	55 (68%)	63 (60%)	0.06
CRi	7 (9%)	4 (4%)	
ORR (CR+CRi)	62 (77%)	67 (64%)	
Early mortality			
Day 30	6 (7%)	5 (5%)	0.46
Day 60	9 (11%)	13 (12%)	0.77
Count recovery in course 1			
Recovered neutrophils to >1.0 x10^9/L	71 (88%)	72 (71%)	0.01
Median days to neutrophil recovery (IQR)	30 (26 - 35)	32 (26 - 39)	0.11
Recovered platelets to >100x10^9/L	58 (72%)	63 (62%)	0.16
Median days to platelet recovery (IQR)	29 (25 - 33)	34 (28 - 44)	<0.01
Count recovery in course 2			
Recovered neutrophils to >1.0 x10^9/L	41 (71%)	55 (83%)	0.09
Median days to neutrophil recovery (IQR)	46 (32 - 52)	31 (26 - 41)	<0.01
Recovered platelets to >100x10^9/L	21 (36%)	39 (59%)	0.01
Median days to platelet recovery (IQR)	36 (35 - 53)	31 (24 - 47)	0.20
Allogeneic transplant			
Allogeneic transplant at any time	36 (44%)	53 (50%)	0.41
Allogeneic transplant in first response*	30 (48%)	43 (64%)	0.10
Outcomes at 3 years			
Overall survival	25%	32%	0.36
Event-free survival	24%	25%	0.86
Relapse-free survival	29%	39%	0.08

*Percentage of those achieving CR/CRi

CR, complete remission; CRi, complete remission with incomplete blood count recovery; IQR, interquartile range; ORR, overall response rate

Figure legends

Figure 1 – CONSORT diagram

Figure 2 – Outcomes by treatment allocation. A) overall survival, B) event-free survival, C) relapse-free survival, D) cumulative incidence of relapse, E) cumulative incidence of death in remission

Figure 3 – Subgroup analyses of overall survival. A) Clinical classification. B) Cytogenetic classification. C) Molecular classification

Figure 4 – Overall survival by randomisation in genomic subgroups. A) MDS-related cytogenetic abnormalities, B) MDS-related gene mutations, C) TP53 mutation

Figure 1

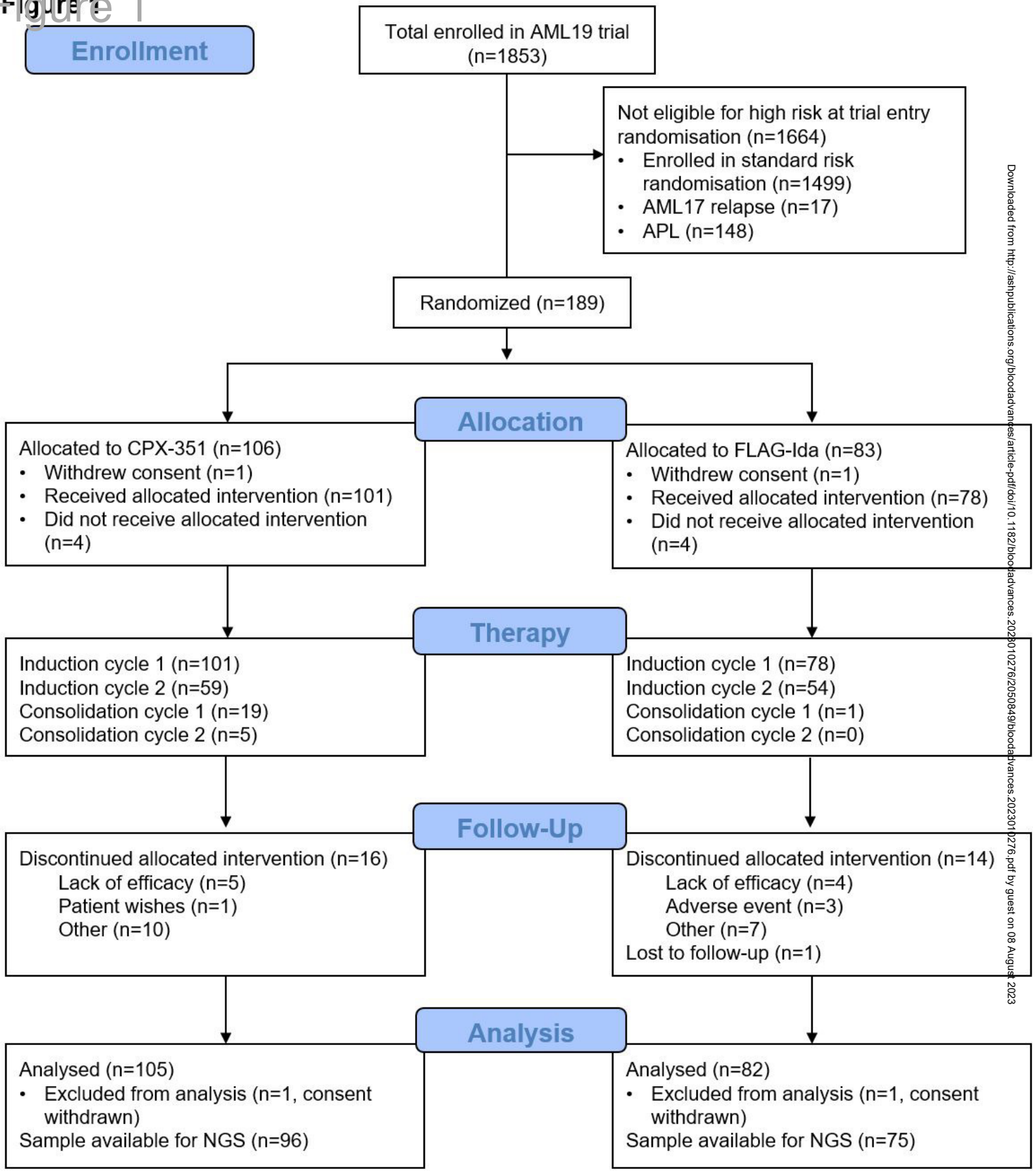
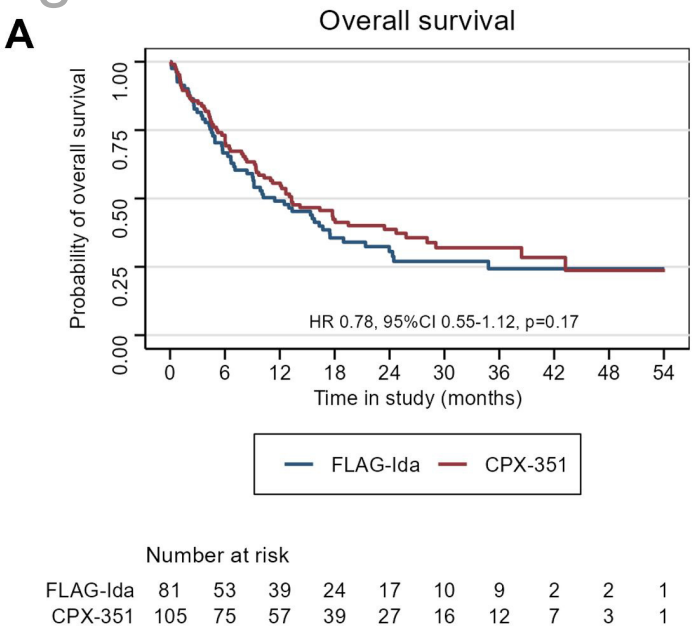
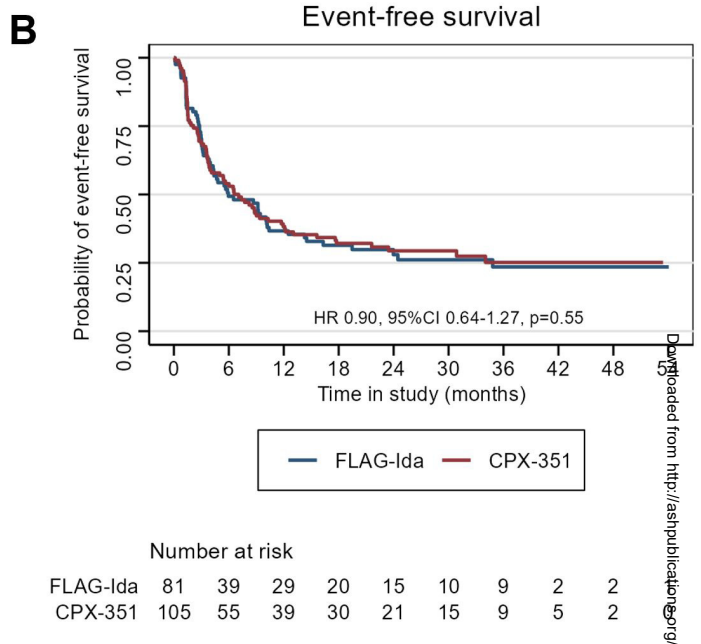


Figure 2



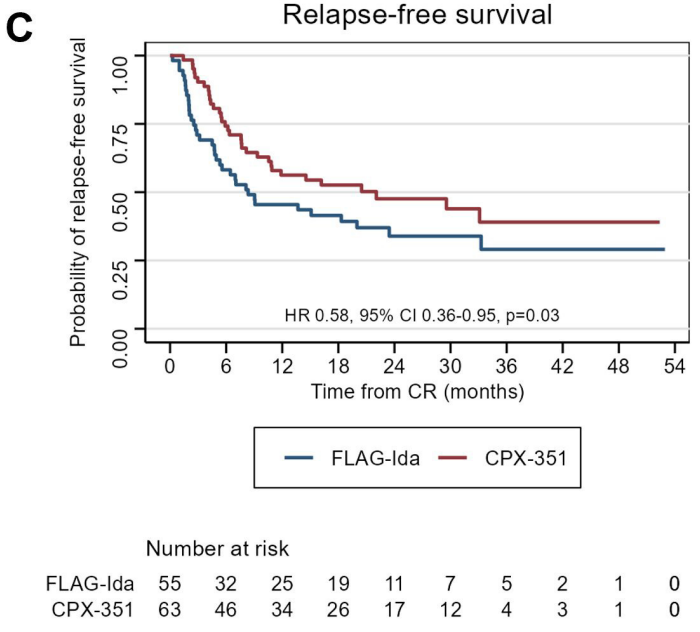
Number at risk

FLAG-Ida	81	53	39	24	17	10	9	2	2	1
CPX-351	105	75	57	39	27	16	12	7	3	1



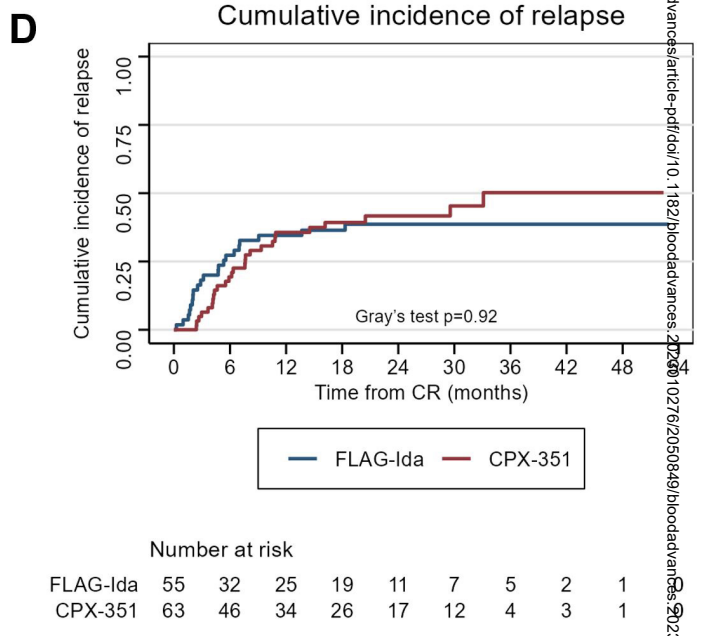
Number at risk

FLAG-Ida	81	39	29	20	15	10	9	2	2	
CPX-351	105	55	39	30	21	15	9	5	2	



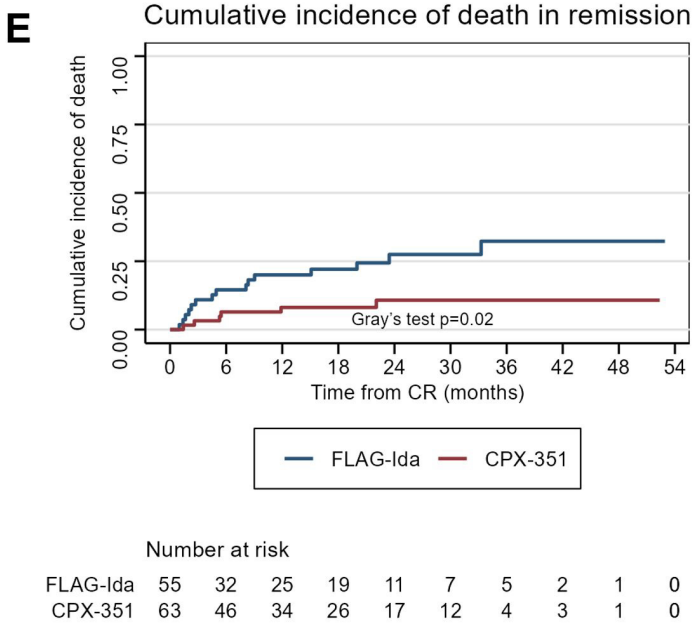
Number at risk

FLAG-Ida	55	32	25	19	11	7	5	2	1	0
CPX-351	63	46	34	26	17	12	4	3	1	0



Number at risk

FLAG-Ida	55	32	25	19	11	7	5	2	1	0
CPX-351	63	46	34	26	17	12	4	3	1	0



Number at risk

FLAG-Ida	55	32	25	19	11	7	5	2	1	0
CPX-351	63	46	34	26	17	12	4	3	1	0

Figure 3

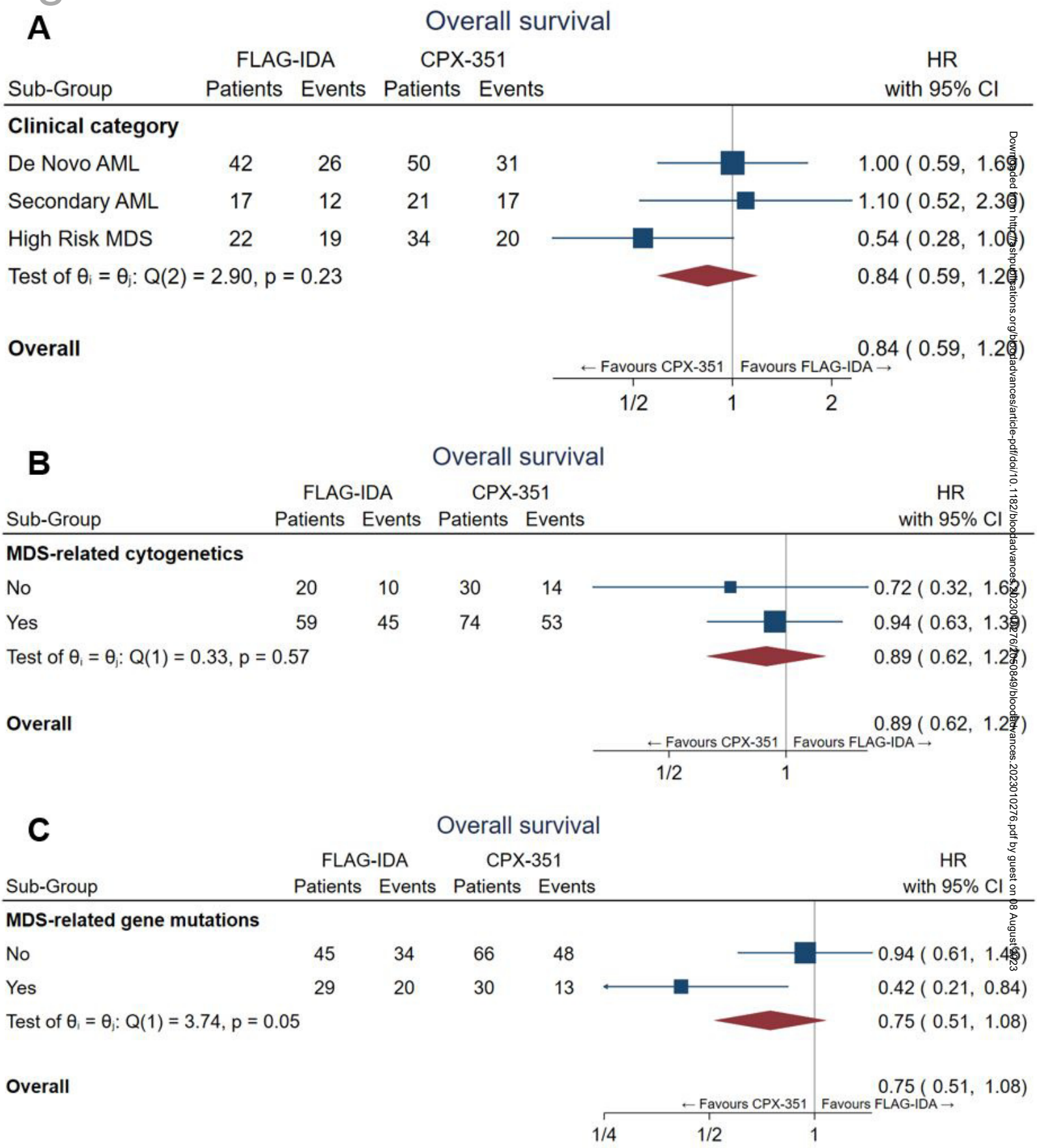


Figure 4