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FLT3 ligand kinetic profile predicts response to treatment in patients with high-risk myelodysplastic syndrome / chronic myelomonocytic leukemia receiving CPX-351: a study from the Groupe Francophone des Myélodysplasies

FLT3 ligand kinetics in CPX-351-treated MDS/CMML

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Study design : PP, JG., PF, and PC ; assays : JG ; patient care and information collection PP, PT, MPG, PYD, ST, AB, SP, MAH, TC, J-M T-G, LD, RS, FC, LA, SD-S, MJ, PF and PC ; data analyses : PP, MJ and PC ; manuscript preparation: PP, PC, MJ. All authors have read and agreed to the manuscript.

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Data sharing

The study details are available online on ClinicalTrials.gov, number NCT04273802. Study data are not publicly available in order to respect participant confidentiality. Requests for sharing deidentified data should be directed to the corresponding author.

Disclosure

The authors have nothing to disclose.

Here, the assessment of soluble Fms-like tyrosine kinase 3 ligand (sFL) kinetics in high-risk (HR) myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) patients during induction therapy with CPX-351, a dual-drug liposomal encapsulation of daunorubicin and cytarabine, showed that both response and event-free survival (EFS) may be predicted by this biological marker.

Therapeutic advances have been limited so far in HR- MDS/CMML.[1,2,] However, highly promising results have recently been published by our group for these patients, testing CPX-351, as first-line induction chemotherapy (GFM-CPX-MDS trial; NCT04273802), with 87% of overall response rate (ORR) and 93.5% of patients bridged to allogeneic hematopoietic stem cell transplant (Allo-HSCT).[3] Here we were interested to study the impact of kinetic profiles of two biological markers, IL-6 and sFL, as part of an ancillary analysis of this prospective study. Indeed, it has been shown, at Nantes University Hospital, that specific kinetic profiles of IL-6 and, mostly, sFL predict refractoriness to induction chemotherapy and, most importantly, overall survival (OS) in acute myeloid leukemia (AML).[4,5] FL is one of the key regulators of hematopoiesis.[6] Yet, the role of FL in MDS or CMML has been poorly investigated so far, as only one study considered this parameter in MDS patients.[7]
Integrating the characterisation of "immunome" in the stratification of MDS/CMML setting may be also of interest to predict outcomes in both diseases as dysregulation of the immunological environment has been proved to play an important role in their pathogenesis.[8–10] For example, in MDS, higher levels of CXC10, IL-6, IL-7[11] or IL-4[12] or C-reactive protein (CRP)[13] have been reported to be associated with shorter survival. In CMML, levels of such pro-inflammatory cytokines as IL-8, TNF-α, IL-6 or IL-4 are significantly elevated, while patients with decreased levels of the immunosuppressive cytokine IL-10 present with a poorer overall survival (OS).[14] Finally, high CRP values are also associated with poorer survival in CMML.[15]

For the purpose of the study, the 31 patients (HR-MDS n=26; HR-CMLL n=5) of the GFM-CPX MDS trial, were considered. Patients received, as first line therapy, intravenous CPX-351 (100 mg/m² cytarabine and 44 mg/m² daunorubicin) on days (D) 1, 3, and 5, with a second induction cycle (same daily dose on days 1 and 3) if at least a partial response was not reached. Patients who responded could receive up to four monthly consolidation cycles (same daily dose on day 1) or Allo-HSCT. One of the secondary objectives of the trial was to evaluate the levels of sFL, IL-6 and CRP, during the first cycle of CPX-351 induction chemotherapy. The trial was approved by an ethics committee (Comité de Protection des Personnes Sud Méditerranée #1994) and the French National Agency for Medicines and Health Products Safety. All patients provided informed consent for this biological sub-study.

Plasma sFL concentrations (pg/mL) were evaluated using a Milliplex® cytokine assay (HCYTA-60K-01, Merck Millipore, Germany), on D1, D8, D15 and D22. Plasma IL-6 levels (pg/mL) were evaluated by ELISA (DY206, Bio-Techne, USA) on D1 and D22, as were those of CRP (mg/L, normal range 0-5; Tina-quant C-Reactive Protein IV, Cobas, Roche Diagnostics, Boulogne Billancourt, France). Both the concentrations and kinetic profile of each parameter were considered to assess their impact on outcome. Responses, including complete remission (CR), CR with incomplete hematopoietic recovery (CRi), morphological leukemia-free state (MLFS), relapse or stable disease (SD), as well as event-free survival (EFS) and OS were evaluated, according to European LeukemiaNet (ELN) 2017 criteria.[16] The new revised International Working Group (IWG) 2023 response criteria for HR/MDS[17] was also used. OS was defined as the time between D1 of CPX-351 administration and the date of death or last follow-up (FU). EFS was defined as the time between D1 of CPX-351 administration and the date of relapse, progressive disease from non-response after 1 or 2 cycles of CPX-351, death or date of last FU.
Patients received the first cycle of CPX 351 between April 29, 2020, and February 10, 2021, and were followed until May 15, 2024. Univariate and multivariate analyses were performed in May 2024 with adjustments for potential confounding factors using the R software (version 4.4.0). All tests were two-sided and p values <0.05 were considered as indicating a statistically significant association.

Clinical results of the whole cohort (n=31) have been already reported.[3] None of the 31 patients had a FLT3 mutated gene. The characteristics of patients who could be evaluated for peripheral blood levels assays (n=28) are provided in Table 1.
According to the ELN2017 criteria, the ORR (CR+CRi+MLFS) after cycle 1 regarding these 28 patients was 86% (n=24; CR+CRi n=17, MLFS n=7), while 4 patients reached SD. Three out of these 4 non-responders received a second induction and 1 achieved CR after cycle 2. According to the more recent IWG 2023 criteria, the ORR after cycle 1 was slightly lower at 75% (n= 21, CR n = 10 + $CR_{bilineage}$ n = 4 +$CR_{unilineage}$ n = 1 +CRh n = 4, PR n= 2).
Most patients (n=26, 93%) received Allo-HSCT after cycle 1 or 2. Among CR/CRi patients, 2 had relapsed and 1 had evolved towards MLFS status before transplant while 2 were not transplanted because of a poor general condition. Among patients in MLFS before transplant, 1 had evolved towards CRi and 2 had relapsed, including one who obtained CRi after salvage regimen. Finally, among SD patients, 1 had obtained CR after salvage regimen before transplant. Thus, at transplant (n=26), 15 patients were in CR/CRi, 5 in MLFS, 3 in SD and 3 with active disease. Relapse occurred in 4 patients after transplant and in 1 non–transplanted patient. Overall, 9 relapses were documented. Median FU, calculated using the reverse Kaplan-Meier estimator, was 40.4 months (95% confidence interval [CI] 39.05-

42.13). With a longer FU than in the previous report[3], the three-year EFS is 46% (95%CI 31-69), and 3-year OS 68% (95%CI 53-88) (Figure 1).
At last FU, 9 patients have died, including one non-transplanted patient who relapsed, and 8 of the 26 transplanted patients, from graft versus host disease (n=3), infection (n=1), relapse (n=3) or multiorgan failure after graft failure (n=1). All patients experimented at least one episode of febrile neutropenia during the first induction. Achieving CR/CRi after the first induction was associated with a better 3-year EFS (59% [95%CI 40-88] vs. 27% [95%CI 10-72]; p=0.043) but not 3-year OS (71% [95%CI 52-96] vs. 64% [95%CI 51-100], p=0.7). Patients transplanted in CR/CRi had the same 3-year OS as those transplanted in MLFS/SD/active disease (80% [95%CI 62-100] vs. 55% [95%CI 32-94], p=0.13).

Median (interquartile range, IQR) plasma sFL concentrations were 4 pg/mL (3- 9) at D1, 74 pg/mL (21-134) at D8, 3267 pg/mL (199-390) at D15 and 381 pg/mL (183-460) at D22.
As in AML,[1] patients could be categorized according to three plasma sFL concentration kinetic profiles: i) sustained increase from D1 to D22 (FLI (sFL sustained Increase) group n=17, 61%), ii) increase from D1 to D15, then decrease on D22 (FLD (sFL increase then Decrease) group, n=9, 32%) and iii) persistent low levels (<100 pg/mL from D1 to D22, FLL (sFL persistent Low levels) group, n=2). Median (IQR) plasma IL-6 concentrations were 11 pg/mL (3-292) on D1 and 180 pg/mL (21-341) on D22. An increase in IL-6 levels between D1 and D22 was observed in 19 patients (68%), a decrease in 7, while 2 patients had no IL-6 detectable at either time. Finally, median (IQR) CRP concentrations were 2 mg/mL (1-4) on D1 and 40 mg/mL (18-98) on D22. An increase in CRP concentrations was observed in most patients between D1 and D22 (n=25, 96%). There was no correlation between IL-6 and CRP concentrations on D1 (p=0.64) or D22 (p=0.48). Of note, no relationship was found between IL-6 or CRP with sFL on both times either.

Relapses occurred in 4, 4 and 1 patients in the FLI, FLD and FLL groups, respectively. Neither CR/CRi rates, 3-year EFS nor OS were correlated with sFL levels (<vs.≥ median) at the 4 time points considered. However, an FLD kinetic profile was significantly associated with higher CR/CRi rates (100% vs. 47% for FLI vs. 0% for FLL; p=0.012) and 3-year EFS (56%, [95%CI,31-100] vs. 47% [95%CI 28-78] for FLI vs. 0% for FLL; p=0.002; Figure 2). Three-year OS was similar between the 3 sFL kinetic profile groups (FLD 67% [95%CI 42-100] vs. 71% [95%CI 52-96] for FLI vs. 50% [95%CI 13-100] for FLL; p=0.8).
In multivariate analysis, considering age, gender, Revised International Scoring System (R-IPSS) and sFL kinetics, an FLD profile was the only factor associated with a higher CR/CRi rate (Odds Ratio [OR]: 25.3, [95%CI 2.02-3843], p=0.004). The same analysis, using the molecular M-IPSS instead of R-IPSS, yielded the same significant isolated value of the FLD

profile (OR: 68.3, [95%CI 3.31-13232], p=0.003; supplemental Figure 1). The poor outcome of the two FLL patients seems independent of baseline characteristics as they had low and high IPSS-M risk, respectively. Plasma concentrations (<vs.≥ median) and IL-6/CRP kinetic profiles had no impact on CR/CRi rates, EFS nor OS. Of note, all the 28 patients were treated with antibiotics during induction in relation with a neutropenic fever, suggesting that its influence on IL6 and CRP level disparities among patients is probably mild.

As already shown in AML,[4] the plasmatic sFL kinetic profile was found here to predict response and EFS in HR-MDS/CMML. However, OS was not impacted by this factor, essentially because Allo-HSCT, that was performed in almost all patients, could clearly reverse the bad outcome linked to a HR sFL kinetic profile. In parallel, we failed to demonstrate any impact of IL6 or CRP in this series, suggesting that other markers probably contribute to the complex mechanisms of immune dysregulation and inflammation during MDS/CMML evolution.

In conclusion, our study suggests that sFL kinetics should be more largely investigated, at least in patients not eligible for Allo-HSCT, as this new biomarker could help to adapt further management to the individual profile of each patient.

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Table 1. Patient characteristics and response to one cycle of CPX-351

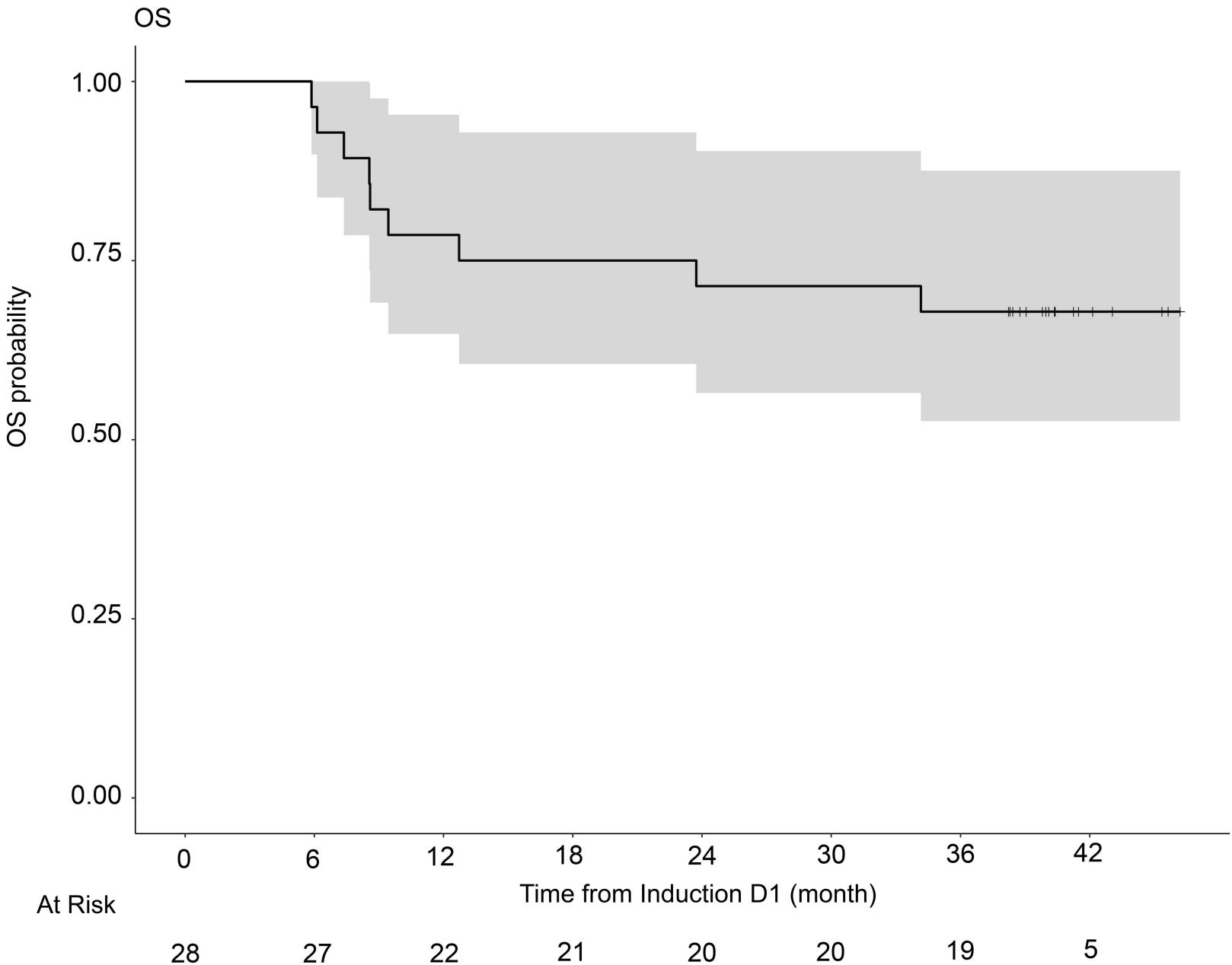
N=28	
Age at diagnosis, years, median (IQR)	62.5 (58-66)
Sex Female/Male, n	9/19
Bone marrow blasts, median (IQR)	13% (IQR 11-15.25)
HR-MDS /HR-CMML, n	23/5
IPSS, n	
Intermediate 2	24
High	4
IPSS-R, n	
Intermediate	9
High	14
Very High	5
IPSS-M, n	
Low	2
Moderate Low	2
Moderate High	6
High	6
Very High	12
GFM CMML model	
Low	3
Intermediate	1
High	1
CPSS-Mol, n	
Intermediate 1	1
Intermediate 2	2
High	2
Responses to cycle 1,[1] n	
CR/CRi	17
MLFS	7
SD	4
Number of CPX-351 consolidation cycles, n	
1 cycle	15
2 cycles	7
3 cycles	3
4 cycles	1
Allo-HSCT, n	26
Median time between cycle 1 and Allo-HSCT, days (IQR)	118 (93-173)
Status at transplant, n	
CR/CRi	15
MLFS	5
SD	3
Progression	3

[1]ELN 2017 Criteria; IQR: interquartile range;HR: high-risk; MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia; IPSS: international prognostic scoring system; R-revised; M: molecular; GFM CMML model: Groupe Francophone des Myelodysplasie; CPSS-Mol: CMML-specific prognostic scoring system; Mol: molecular; CR: complete response; Cri: complete response with incomplete hematological recovery; MLFS: morphological leukemia-free state; SD: stable disease; HSCt: hematopoietic stem cell transplantation.

Figure legends

Figure 1. Overall survival of the whole cohort.
ASCT: allogeneic hematopoietic stem cell transplantation.

Figure 2. Event-free survival according to the three kinetic profiles of plasma soluble Flt3-ligand. FLD: sFL concentration increase until day 15, then decrease; FLI: sFL concentration sustained increase from day 1 to day 22; FLL: sFL concentration persistent low levels.


OS
1.00
0.75
0.50
0.25
0.00
OS probability
0
6
12
18
24
30
36
42
Time from Induction D1 (month)
At Risk
28
27
22
21
20
20
19
5

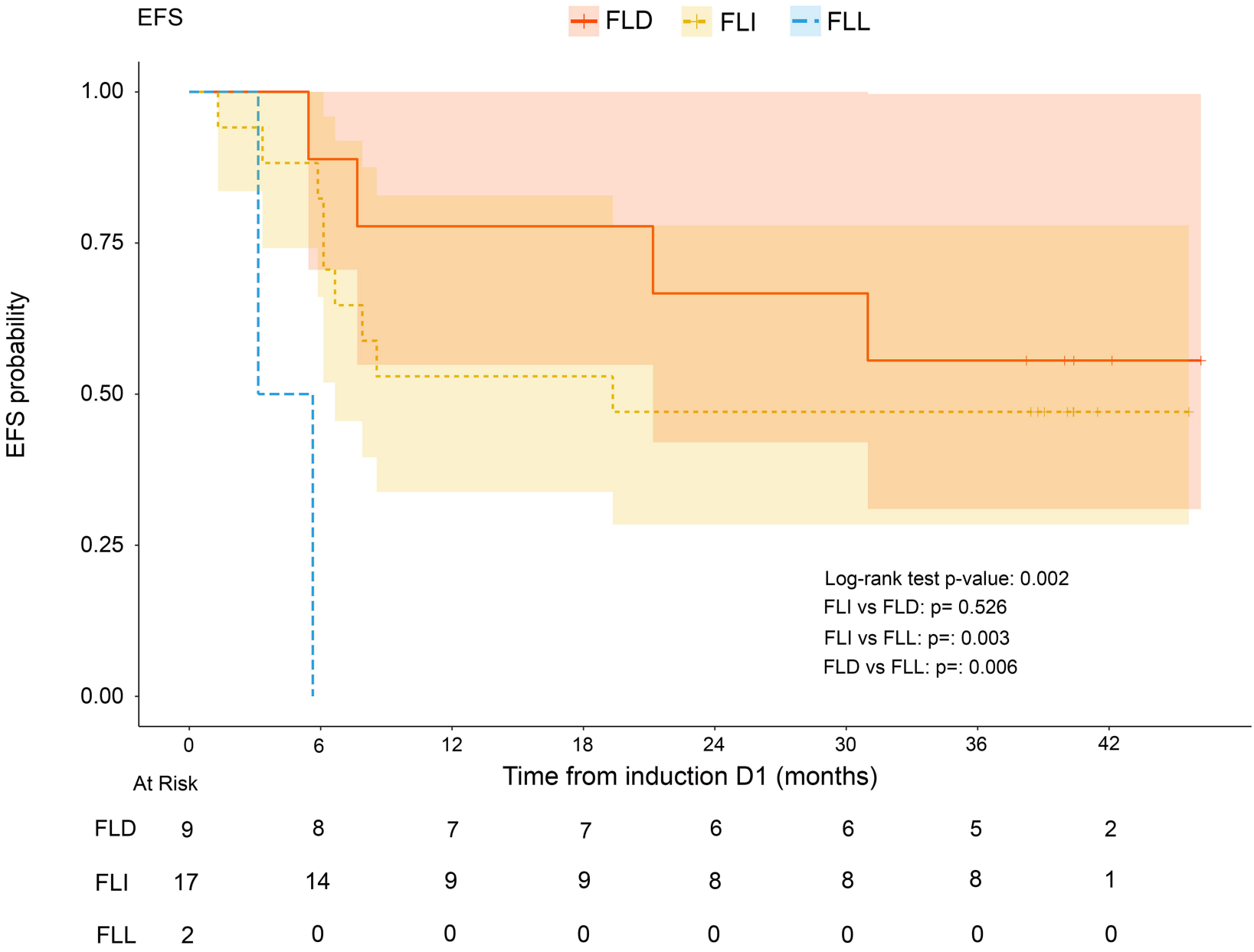

EFS
FLD
FLI
FLL
1.00
0.75
0.50
0.25
0.00
EFS probability
Log-rank test p-value: 0.002
FLI vs FLD: p= 0.526
FLI vs FLL: p=: 0.003
FLD vs FLL: p=: 0.006
0
6
12
18
24
30
36
42
Time from induction D1 (months)
At Risk
FLD 9 8 7 7 6 6 5 2
FLI 17 14 9 9 8 8 8 1
FLL 2 0 0 0 0 0 0 0

Figure legends

Supplemental figure 1. Forest plot of multivariate analysis.
sFL: soluble Flt3-ligand; FLI: sustained increase from day 1 to day 22; FLD: increase until day 15, then decrease; FLL: persistent low levels; F: female; M: male; IPSS-M: Molecular International Prognostic Scoring System; L:low; H:high;VH: very high; OR: odds ratio.

Supplemental figure 1