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SUPPLEMENTAL METHODS

Patient selection
We identified patients at our institution who had a diagnosis of “therapy-related myeloid neoplasm” or “AML with myelodysplasia-related changes” and who had received treatment with CPX-351. The drug was provided by St. Jude Children’s Research Hospital after a non-protocol treatment plan had been approved. The cutoff for retrospective data analysis was April 30, 2021. This study has been approved by the Institutional review board approval of St. Jude Children’s Research Hospital (BMFD #19-0375) and was conducted in accordance with the Declaration of Helsinki.

Treatment and evaluations
CPX-351 was administered at a dose of 100 units/m² (corresponding to cytarabine 100 mg/m² and daunorubicin 44 mg/m²) on days 1, 3, and 5 of each cycle to six patients with newly diagnosed sMDS/AML. The number of cycles of CPX-351 was determined based on the response to the first course, the cumulative dosage of anthracycline in patients previously treated for their primary cancers, and the expected timing of hematopoietic cell transplantation (HCT). Decitabine, azacytidine, venetoclax, and gilteritinib were used to bridge to HCT (Table 1 and Figure 1A). Patients 1, 4, 5, and 7 received haplo HCT on institutional protocols. Assessment of morphology and cellularity, along with metaphase karyotyping, FISH cytogenetics, and flow cytometry, were performed in bone marrow (BM) before and after each cycle of CPX-351. The measurable residual disease (MRD) flow cytometry assay had a sensitivity of 0.1% (= 10 in 10,000 cells). MRD of at least 0.1% was defined as positive, whereas MRD of less than 0.1% was considered negative.

Toxicity
Toxicity events were retrospectively graded using version 4 of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAEv4). Any grade 3 or higher non-hematologic adverse events related to CPX-351 were annotated (Table S3). The ejection and shortening fractions were derived from an echocardiogram obtained at baseline for each cycle and before HCT. Commonly occurring complications during initial AML presentation and treatment unrelated to CPX-351 were not classified.

Genomic studies
Clinical cancer genomic profiling was performed by institutional three-platform sequencing of the whole genome, whole exome, and transcriptome (RNA sequencing) in BM specimens and in fibroblasts used as germline control, as previously reported1. Genome sequencing files were analyzed for the presence of potential pathogenic germline variants by using the PeCanPIE (Pediatric Cancer Variant Pathogenicity Information Exchange: https://pecan.stjude.cloud/pie) pipeline as recently published2. In addition, targeted sequencing for germline predisposition and/or somatic mutations associated with MDS/AML was performed in CLIA-certified laboratories (Table S2).
CASE SUMMARIES

Details of the therapeutic procedures and serial hematologic evaluations are provided in Table S1. Table S2 has details of the clinical presentation, cytogenetics, and genomic findings, and Table S3 presents data on toxicity.

PATIENT 1 is a 13-year-old boy with a history of localized left femur osteosarcoma treated with methotrexate, cisplatin, and doxorubicin. Two years after completion of therapy, he was noted to have neutropenia, macrocytic anemia, and myeloblasts in the peripheral blood. Therapy-related AML was diagnosed, with 60% myeloid blasts in the BM. Genomic studies revealed abnormal cytogenetics, with gains or losses of chromosomal material and a translocation t(2;3) involving MECOM (Table S2). In addition, somatic mutations were found in the KRAS, IKZF1, NF1, and CSNK1A1 genes, along with a germline heterozygous variant of uncertain significance (VUS) in the FANCD2 gene. This FANCD2 variant is present in five gnomAD controls and has not been reported previously in patients with Fanconi anemia.

BM evaluation after the first cycle of CPX-351 treatment revealed hypocellular BM (5%-10%) with a decrease in blasts from 60% before treatment to 20% after treatment, which is consistent with PR (Table S1). After the second cycle of CPX-351, no blasts were detected in the BM based on morphology, whereas flow cytometry showed 0.22% blasts. Two weeks later, in preparation for HCT, the percentage of BM blasts measured by flow cytometry increased to 1.44%. The patient underwent haploidentical HCT (protocol HAPNK1, NCT#01807611) with his father as the donor and remained in remission for 12 months. BM evaluation performed 12 months after HCT and 14 months after diagnosis revealed leukemia relapse (with 5.6% blasts by flow cytometry and recurrence of abnormal cytogenetics). No response was observed after treatments with decitabine and venetoclax with cytarabine. The patient then underwent a second haploidentical HCT from his mother (protocol REF2HCT, NCT#02790515) and remains in remission more than 1.5 years after the second HCT.

CPX-351 toxicity (Table S3): Grade 3 maculopapular rash during the first cycle of CPX-351.

PATIENT 2 is a 19-year-old man in whom localized osteosarcoma of the left tibia was diagnosed at the age of 14 years. He was treated with cisplatin, doxorubicin, high-dose methotrexate, ifosfamide, etoposide, and G-CSF and underwent surgical resection of his tibial lesion. Four years off therapy, two pulmonary nodules were noted on his routine CT scan. During his evaluation for pulmonary metastasis, 20% myeloid blasts were present in the peripheral blood and 47% in the BM, and a diagnosis of secondary AML was established in addition to osteosarcoma relapse. Genomic studies performed in the BM identified an abnormal karyotype [46,XY,del(11)(p11.2p15.2)], inversion of chromosome 3 with MECOM upregulation, and a translocation t(5;5) involving the NIM1K and TERT genes. In addition, a somatic WT1 mutation was detected (Table S2).

The patient received two courses (10 days each) of decitabine, resulting in a PR (22% BM blasts) (Table S1). He then received the first cycle of CPX-351 and after 4 weeks showed CR with a decrease in BM blasts to 3%. After a further 2 weeks of observation, he attained CR with MRD-negative status (as assessed by flow cytometry). During this period, he underwent resection of the osteosarcoma metastasis in his left lung. The postoperative course was complicated by a seroma at the incision site that
resolved within 17 days. Treatment proceeded with a second cycle (two doses) of CPX-351. After hematologic recovery, the patient underwent resection of the right lung metastasis and subsequently had a prolonged bacterial wound infection that delayed the HCT. After the resolution of the wound infection, he was reassessed for response at day 55 after the start of the second CPX-351 cycle. BM analysis revealed 6% blasts by morphology and 20% by flow cytometry. The patient received a third cycle (three doses) of CPX-351 and attained a PR (5% BM blasts by morphology, 6.99% by flow). He proceeded to undergo haploidentical HCT (with his brother as the donor), and he has been disease-free for both the osteosarcoma and sAML for more than 3 years since undergoing HCT.

**CPX-351 toxicity** (Table S3): Grade 3 febrile neutropenia without complications during the first two cycles of CPX-351, otherwise grade 3 maculopapular rash during all cycles.

**PATIENT 3** was a 23-year-old man with a history of treatment for localized Ewing sarcoma, originally diagnosed when the patient was aged 18 years. He received vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide, along with radiation therapy to his primary site. One year after completion of treatment, the patient presented with local recurrence. He was then treated with cyclophosphamide/topotecan, followed by autologous HCT and re-irradiation of the left ilium. Two years later, the patient was noted to have pancytopenia, with 0.8% myeloblasts and a number of dysplastic myeloid cells in the peripheral blood. BM evaluation showed 56% myeloblasts with MDS morphology. Further molecular examinations revealed a karyotype with multiple chromosomal gains and losses; copy-number changes involving the KMT2A, ATM, ETV6, and CSNK1A1 genes; somatic mutations in TP53, NF1, and PDGFRα; and a heterozygous germline VUS in HLTF (p.Y538S). This HLTF variant is present in one gnomAD control and, thus far, has not been associated with disease (Table S2). Previously, a germline HLTF p.E259K mutation was described in a family with adult-onset MDS and was experimentally shown to reduce the binding capacity of HLTF with ubiquitin-conjugating enzymes, resulting in impaired polyubiquitination of PCNA.

After the first cycle of CPX-351, the patient attained CRi with a decrease in blasts from 56% before treatment to 3% after treatment. Early complications during this first cycle of CPX-351, included fever and respiratory distress, which were attributed to the initial disease manifestation. His respiratory status deteriorated, and he was intubated and mechanically ventilated. Blood cultures were positive for *Staphylococcus epidermidis*. He also developed acute kidney injury. He recovered from these complications and received the second cycle of CPX-351, which was well tolerated. Evaluation after the second cycle of CPX-351 revealed a marked hypocellular marrow (<5%) and MRD of 0.15%. HCT was delayed because of difficulty in identifying a suitable donor and an adult transplantation center. Although the patient’s WBC counts were slowly recovering, he was dependent on platelet and erythrocyte transfusions. On day 53 after the initiation of the second CPX-351 cycle, a 10-day course of decitabine was initiated. Repeat evaluation 7 days after the completion of decitabine showed complete replacement of the BM by leukemia cells (98%). The patient was treated with low-dose cytarabine and a FLAG regimen, after which he developed multi-organ failure and expired 4 months after the diagnosis of sAML.

**CPX-351 toxicity** (Table S3): Grade 3 febrile neutropenia without complications during both cycles of CPX-351.

**PATIENT 4** is a 16-year-old boy previously treated for high-risk (MYCN amplified), stage IV neuroblastoma...
that was diagnosed when the patient was aged 2 years. His treatment consisted of intensive systemic chemotherapy followed by myeloablative chemotherapy and autologous HCT, left adrenalectomy, and retroperitoneal radiation therapy. Fifteen years after the completion of neuroblastoma treatment, the patient developed clinical and laboratory signs and symptoms of mononucleosis. During follow-up of this process, anemia and thrombocytopenia manifested and leukemia blasts were detected on the peripheral blood differential. BM evaluation revealed AML with monoblastic differentiation, 71% blasts by morphology, and a complex karyotype involving del(5q). Molecular studies have identified a germline heterozygous pathogenic mutation in the CHEK2 gene (p.R117G). This mutation is not present in gnomAD controls, has been previously reported in families with breast cancer, and has been shown to be a deleterious mutation causing impaired phosphorylation and loss of the CHEK2-mediated DNA damage response.

The patient received one cycle of CPX-351 and attained complete remission with MRD of less than 0.1% and 2% blasts on morphologic examination. He proceeded to undergo haploidentical HCT with his sister as the donor (protocol HAP2HCT, NCT#03849651). At the last follow-up, the patient was 6 months post HCT and was engrafted with 100% donor chimerism.

CPX-351 toxicity (Table S3): Grade 3 febrile neutropenia without complications, maculopapular rash, and oral mucositis during CPX-351 treatment.

Patient 5 is an 18-year-old woman treated for T-cell acute lymphoblastic leukemia with a pseudodiploid karyotype on the St. Jude Total XVI protocol. In her routine evaluation at 2 years off therapy, she was found to have thrombocytopenia with an increased white blood cell count but without constitutional symptoms. BM evaluation showed 57% myeloblasts by morphology and 11% blasts by flow cytometry, leading to the diagnosis of sAML. Genomic studies revealed monosomy 7 and somatic NF1 and RUNX1 mutations.

The patient received two cycles of CPX-351. After the first cycle, her BM was hypocellular (20%-30%), with 34% blasts by morphology and 5.98% by flow cytometry (Table S1). Forty-five days after the second cycle of CPX-351, the BM was normocellular without blasts by morphology and with residual disease of 0.29% by flow cytometry. The patient maintained remission before undergoing haploidentical HCT with her maternal uncle as the donor (protocol HAPNK1, NCT#01807611). After HCT, she received monthly azacytidine for 10 months. She was in remission at the last follow-up, 34 months post HCT.

CPX-351 toxicity (Table S3): Grade 3 febrile neutropenia without complications and maculopapular rash during both CPX-351 cycles.

Patient 6 is a 17-year-old boy with Cornelia de Lange syndrome associated with a germline heterozygous SMC3 splice-site mutation c.430-1G>T that causes an in-frame deletion of three amino acids, as confirmed by RNA-seq (Table S2). Previous constitutional features included nonverbal developmental delay, hearing impairment, microcephaly, micrognathia, and G-tube dependence. The patient was admitted at the age of 17 years for macrocytic anemia and thrombocytopenia (Hb 3.6g/dL, MCV 117fl, platelets 26 × 10^9/L, WBC 16.5 × 10^9/L). Myeloblasts with Auer rods were found in the peripheral blood (7% on smear and 5% by flow cytometry). Other abnormalities included megaloblastic erythroid progenitors and dysplastic granulocytes. BM evaluation was consistent with MDS-EB-2 (6% blasts with Auer rods), and the patient was referred to St. Jude for HCT. The MDS progressed rapidly, with an increasing WBC count (59.0 × 10^9/L)
and peripheral blast count (35%). The BM was hypercellular, with prominent dysplastic findings and 24% blasts, some with Auer rods (Table S1). Genomic studies revealed a normal karyotype, and the presence of somatic mutations in \textit{NRAS}, \textit{CEBPA}, \textit{NPM1}, and \textit{FLT3}-ITD was noted.

Because of hyperleukocytosis, the patient received three doses of i.v. cytarabine at 100 mg/m^2/q12 hours, followed by a cycle of CPX-351. On day 25 after the start of CPX-351 therapy, his BM was hypocellular with no evidence of blasts, consistent with CRi (Table S1). Residual leukemia (MRD) as measured by flow cytometry was 0.07%. On a repeated BM exam 2 weeks later, MRD had increased to 0.23% whereas the WBC and platelet counts were recovering. Because his leukemia cells harbored a somatic \textit{FLT3}-ITD lesion found at diagnosis, the patient was started on gilteritinib (an orally available small molecule inhibitor of FLT3 tyrosine kinase) as a bridge to HCT. He tolerated the medication well and experienced complete hematologic recovery with no detectable blasts and with negative MRD (Table S1). He then underwent an HLA-matched (10/10) unrelated donor HCT. Gilteritinib was re-started on day +100 post HCT. The patient is tolerating gilteritinib well and has no evidence of disease at 6 months after HCT.

**CPX-351 toxicity** (Table S3): Grade 3 febrile neutropenia without complications and maculopapular rash during administration of CPX-351.

**PATIENT 7** is a previously healthy 13-year-old girl who presented with a 2-week history of malaise, abdominal pain, and acute development of nausea, vomiting, and fever. She was found to be hypotensive, tachycardic, and febrile. She quickly decompensated with multi-organ failure and shock. Blood counts showed an Hb of 3g/dL, a WBC of 5.0 × 10^9/L, a platelet count of 108.0 × 10^9/L, and immature myeloid cells on the peripheral blood differential. The patient was treated with antibiotics, fluids, and vasopressors and was eventually intubated and mechanically ventilated. Inflammatory markers, including ferritin, D-dimer, fibrinogen, C-reactive protein, IL-6, IL-10, tumor necrosis factor, and interleukin-2 receptor, were all elevated. There was no laboratory evidence of past or current SARS-CoV-2 infection that would explain the hyperinflammatory state; furthermore VEXAS syndrome (X-linked UBA1 mutations) has been ruled out. To control the inflammation, the patient received tocilizumab (an IL-6 inhibitor) and intravenous immunoglobulin with no improvement.

BM examination revealed a hypercellular marrow with multilineage dysplasia, overt fibrosis, and increased myeloblasts (32%) with a complex karyotype that involved monosomy 7. In addition, somatic deletions were found in \textit{TP53} (homozygous), \textit{RUNX1}, and \textit{ZBTB7A} (Table S2). No germline variants of potential clinical significance were found by genome sequencing. A diagnosis of AML with MDS-related changes and hyperinflammation was made. Because of persistent multi-organ dysfunction with a hyperinflammatory state, the patient was ineligible for standard AML regimens and was treated with anakinra (an IL-1 receptor antagonist) and glucocorticoids, shortly followed by CPX-351, which led to rapid clinical improvement. BM evaluation at day 22 after CPX-351 initiation revealed hypocellularity and 1.09% blasts as detected by flow cytometry (Table S1). Because of the delay in obtaining an HCT donor, the patient received decitabine (for 5 days) and venetoclax (for 49 days) and remained in complete morphologic remission with rapid recovery of peripheral blood counts. Immediately before HCT, the patient’s BM was normocellular with no signs of myelodysplasia and the MRD was 0.17% by flow cytometry. Of note, conventional karyotyping continued to show occasional metaphases with a complex karyotype including chromosome 7 loss. Inflammatory markers, including TNF, remained elevated. The patient underwent haploidentical HCT with her grandmother as the donor (protocol REF2HCT,
NCT#02790515). Her post-HCT course was complicated by cardiac dysfunction requiring a brief course of milrinone. At the last follow-up, 7 months after HCT, the patient was fully engrafted and clinically well with no evidence of leukemia or GVHD.

**CPX-351 toxicity** (Table S3): no relevant toxicity was noted.
| Patient | Diagnosis of sAML | Complete blood count | Cellularity in BM | MRD by FISH (%) | BM blasts (%) | Post-HCT (months) |
|---------|------------------|----------------------|-------------------|----------------|-------------|-----------------|
| 1       | CPX351 (cycle 1), 100 unit/mL, days 1, 3, 5 | 2.3/0.9 | 60-70%, normocellular | 60 | 35 | 1 month after Dx |
|         | CPX351 (cycle 2), 100 unit/mL, days 1, 3, 5 | 1.6/7.8 | 5%-10%, hypocellular | 20 | 6.35 | 1 month after Dx |
|         | 2 months after Dx | 1.5/7.9 | 5%-10%, hypocellular | 0 | 0.22 | 2.5 months after Dx |
|         | 4 months after HCT | 2.37/8.6 | <5%, markedly hypocellular | 10 | 1.44 | 4 months after HCT |
|         | 6 months after Dx | 4.8/11.2 | 10%-20%, hypocellular | 3 | 5.6 | 6 months after Dx |
|         | 14 months after Dx | 3.76/13.4 | 20%-30%, hypocellular | 3 | 5.6 | 14 months after Dx |
|         | Post-HCT decitabine, 20 mg/m², days 1-10 | 1.54/9.2 | 10%-30%, hypocellular | 6 | 4.16 | 15 months after Dx |
|         | Post-HCT venetoclax, 800 mg, days 1-28+cytarabine, 500 mg/m², days 1-8 | 0.62/7.6 | <5%, markedly hypocellular | 17 | 5.56 | 15.5 months after Dx |
|         | 16 months after Dx | 2.49/7.8 | 40%-50%, mildly hypocellular | 0.077 | 0 | 1 month after Dx |
| 2       | CPX351 (cycle 1), 100 unit/mL, days 1-3 (5 months after Dx) | 29 months after HCT | - | - | - | - |
|         | 5 months after HCT | 10.25/13.3 | <30%, hypocellular | 0 | 0 | - |
| 3       | CPX351 (cycle 1), 100 unit/mL, days 1, 3, 5 | 4.09/10.9 | >90%, hypercellular | 56 | 50 | - |
|         | 1 month after Dx | 3.06/12 | 50%-60%, normocellular | 3 | 6.18 | - |
|         | 2 months after Dx | 13.0/9.0 | Hypocellular | 0 | 0 | - |
|         | 3.5 months after HCT | 1.7/8.9 | 5%-10%, hypocellular | 5 | 6.99 | - |
|         | 9 months after HCT | 6.4/8.4 | <30%, hypocellular | 0 | 0 | - |
|         | 19 months after Hct | 5.15/15.7 | 30%-40%, mildly hypocellular | 0 | 0 | - |
|         | 31 months after Dx | 7.49/15.3 | Normocellular | 0 | 0 | - |
| 4       | CPX351 (cycle 1), 100 unit/mL, days 1, 3, 5 | 0.813/5.4 | Hypocellular | 71 | 34 | - |
|         | 1 month after Dx | 5.08/10.5 | <80%, hypocellular | 2 | 0 | - |
|         | 1.5 months after Dx | 0.69/9.7 | 10%-15%, markedly hypocellular | 2 | 0 | - |
|         | Haplo-HCT (related) | 3.74/9.3 | Normocellular | 2 | 0 | - |
|         | 3.3 months after Dx | 3.9/11.4 | >50%, hypocellular | 57 | 11 | - |
| 5       | CPX351 (cycle 1), 100 unit/mL, days 1, 3, 5 | 0.813/5.4 | Hypocellular | 57 | 11 | - |
|         | 1 month after Dx | 5.08/10.5 | <80%, hypocellular | 2 | 0 | - |
|         | 1.5 months after Dx | 0.69/9.7 | 10%-15%, markedly hypocellular | 2 | 0 | - |
|         | Haplo-HCT (related) | 3.74/9.3 | Normocellular | 2 | 0 | - |
|         | 3.3 months after Dx | 3.9/11.4 | >50%, hypocellular | 57 | 11 | - |
| 6       | CPX351 (cycle 1), 100 unit/mL, days 1, 3, 5 | 0.813/5.4 | Hypocellular | 57 | 11 | - |
|         | 1 month after Dx | 5.08/10.5 | <80%, hypocellular | 2 | 0 | - |
|         | 1.5 months after Dx | 0.69/9.7 | 10%-15%, markedly hypocellular | 2 | 0 | - |
|         | Haplo-HCT (related) | 3.74/9.3 | Normocellular | 2 | 0 | - |
|         | 3.3 months after Dx | 3.9/11.4 | >50%, hypocellular | 57 | 11 | - |
| 7       | CPX351 (cycle 1), 100 unit/mL, days 1, 3, 5 | 0.813/5.4 | Hypocellular | 57 | 11 | - |
|         | 1 month after Dx | 5.08/10.5 | <80%, hypocellular | 2 | 0 | - |
|         | 1.5 months after Dx | 0.69/9.7 | 10%-15%, markedly hypocellular | 2 | 0 | - |
|         | Haplo-HCT (related) | 3.74/9.3 | Normocellular | 2 | 0 | - |
|         | 3.3 months after Dx | 3.9/11.4 | >50%, hypocellular | 57 | 11 | - |
Abbreviations: BM, bone marrow; MRD, measurable residual disease; FCM, flow cytometry; WBC, white blood count; Hb, hemoglobin; PLT, platelet count; ANC, absolute neutrophil count; sAML, secondary acute myeloid leukemia; Dx, diagnosis; Haplo-HCT, haploidentical hematopoietic cell transplantation; sMDS, secondary myeloid dysplastic syndrome; MUD, matched unrelated donor.
### Table S2. Genomic findings at diagnosis of myeloid malignancy.

| Patient | Cytogenetics | Translocations | Germline variants and gnomAD frequency | Somatic mutations | Allele frequency of somatic mutations |
|---------|--------------|----------------|----------------------------------------|------------------|--------------------------------------|
| 1       | 46,XY.add(3)(q29),del(5)(q23q34), del(7)(q22q34)[11]/46,XY[9] | t(2;3)(p21;q26.2)/MECOM | **FANCD2**: c.2765A>G, p.H922R (heterozygous VUS) gnomAD2.1.1: 5/282742 alleles | **KRAS**: c.35G>A, p.G12D **IKZF1**: c.1398T>C, p.*520Q | 11% WGS, 11% WES 14% WGS, 9% WES 11% WGS, 12% WES 4% WGS, 12% WES 5q31.1p33 (130835201-156741200) X 1 |
| 2       | 46,XY.del(11)(p11.2p15.2)[10]/46,XY[10] | inv(3)(p24.3;q26.2)/MECOM t(5;5)(p12;p15.33)/NIM1K | **WT1**: c.1347_1348insGAGGGCCC, p.K450Efs*33 **WT1**: c.1090_1093delTCGG, p.S364Hfs*67 | **TP53**: c.863_864insCATG, p.W288Cfs*12 | 15% WGS, 3% WES 29% WGS, 29% WES |
| 3       | 43,XY,-6,iAMP11q,add(12)(p11.2),-17,-18(11)(44idem, +mar[3]/58,XY, +4,+6,+8,+9,+10,iAMP11q,+12,add(12)(p11.2),+13,+15,+19,+20,+20,+22[3]/46,XY[3] | - | **HLTF**: c.1613A>C, p.Y538S (heterozygous pathogenic) gnomAD2.1.1: not found | **CEBPA**: c.333_334dup, p.P112Rfs*49 | 34% WGS, 29% WES 33% WGS, 31% WES 23% WGS, 27% WES 10% WGS, 22% WES 12p13.33p11.23 (60701-27595900) X 1; 5q13.3q5.3 (75447915-180785400) X 1 |
| 4       | 46,XY.del(5)(q22q33),t(6;13)(q25;q12),inv(10)[q22q26][13]/46,XY[7] | - | **CHEK2**: c.349A>G, p.R117G (heterozygous pathogenic) gnomAD2.1.1: not found | None identified | |
| 5       | 45,XX,-7[20] | - | - | **NF1**: c.1019_1020delCT, p.S340Cfs*12 **RUNX1**: c.861C>A, p.Y287* | 34% WGS, 26% WES 23% WGS, 25% WES 50% WGS, 45% WES |
| 6       | 46,XY[20] | - | - | **SMC3**: c.430-1G>T, p.I144_Q146del, (heterozygous pathogenic), RNAseq confirmed 3-aa in-frame deletion gnomAD2.1.1: not found | **NPM1**: c.863_864insCATG, p.W288Cfs*12 **CEBPA**: c.333_334dup, p.P112Rfs*49 | 34% WGS, 29% WES 33% WGS, 31% WES 23% WGS, 27% WES 10% WGS, 22% WES 3 x in-frame ITD (5aa, 8aa, 15aa), exon 14 |
| 7       | 45,XX,der(6)(6;21)(q13;q22),ins(11;5)(p15;q13q33),del(7)(q22), dic(17;21)[p13;p11.2;21, +der(?)(12;7)[p13;7][42]/44,4idem, -7,der(18)(18pter->18q23::?:7q22- >7qter)[11]/46,XX[6] | - | **TP53** homozygous deletion | **RUNX1** homozygous deletion **ZBTB7A** heterozygous deletion | 17p13.1(7590693_7590942) X 0 21q22.11q22.12(34675412_36456834) X 1 19p13.3(3896264_4052093) X 1 |

**Abbreviations:** gnomAD, genome Aggregation Database; VUS, variant of uncertain significance; WGS, whole-genome sequencing; WES, whole-exome sequencing; amp, amplification; aa, amino acid.
Table S3. Grade III or higher toxicity during CPX-351 treatment courses.

| Adverse events                  | Cycle 1 (n = 7) | Cycles 2 and 3 (n = 5) |
|---------------------------------|-----------------|------------------------|
|                                 | n   | %    | n   | %   |
| Febrile neutropenia (grade III) | 5    | 71   | 3    | 60  |
| Rash (grade III)                | 5    | 71   | 3    | 60  |
| Oral mucositis (grade III)      | 1    | 14   | -    | -   |

Abbreviation: CTCAEv4, common terminology criteria for adverse events version 4.
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