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Time from diagnosis to treatment has no impact on survival in newly diagnosed acute myeloid leukemia treated with venetoclax-based regimens

by David Baden, Sven Zukunft, Gema Hernandez, Nadine Wolgast, Sophie Steinhäuser, Alexander Pohlmann, Christoph Schliemann, Jan-Henrik Mikesch, Björn Steffen, Tim Sauer, Maher Hanoun, Kerstin Schäfer-Eckart, Stefan W. Krause, Mathias Hänel, Hermann Einsele, Edgar Jost, Tim H. Brümmendorf, Sebastian Scholl, Andreas Hochhaus, Andreas Neubauer, Andreas Burchert, Martin Kaufmann, Dirk Niemann, Markus Schaich, Wolfgang Blau, Alexander Kiani, Martin Görner, Ulrich Kaiser, Johannes Kullmer, Thomas Weber, Wolfgang E. Berdel, Gerhard Ehninger, Carsten Müller-Tidow, Uwe Platzbecker, Hubert Serve, Martin Bornhäuser, Christoph Röllig, Claudia D. Baldus, and Lars Fransecky

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Time from diagnosis to treatment has no impact on survival in newly diagnosed acute myeloid leukemia treated with venetoclax-based regimens

David Baden[1,2,#], Sven Zukunft[3], Gema Hernandez[4], Nadine Wolgast[1,2], Sophie Steinhäuser[1,2], Alexander Pohlmann[5], Christoph Schliemann[5], Jan-Henrik Mikesch[5], Björn Steffen[6], Tim Sauer[7], Maher Hanoun[8], Kerstin Schäfer-Eckart[9], Stefan W. Krause[10], Mathias Hänel[11], Hermann Einsele[12], Edgar Jost[13], Tim H. Brümmendorf[13], Sebastian Scholl[14], Andreas Hochhaus[14], Andreas Neubauer[15], Andreas Burchert[15], Martin Kaufmann[16], Dirk Niemann[17], Markus Schaich[18], Wolfgang Blau[19], Alexander Kiani[20], Martin Görner [21], Ulrich Kaiser[22], Johannes Kullmer[23], Thomas Weber[24], Wolfgang E Berdel[5], Gerhard Ehninger[3], Carsten Müller-Tidow[7], Uwe Platzbecker[25], Hubert Serve[6], Martin Bornhäuser[3], Christoph Röllig[3], Claudia D Baldus[1,2], Lars Fransecky[1,2]

[1] Department of Internal Medicine II, University Hospital Schleswig-Holstein, Kiel, Germany

[2] University Cancer Center Schleswig-Holstein, University Hospital Schleswig-Holstein, Kiel, Germany

[3] Medical Department I, University Hospital of TU Dresden, Dresden, Germany

[4] TriNetX, TriNetX Europe NV, Sint-Martens-Latem, Belgium

[5] Department of Medicine A, University Hospital Münster, Germany

[6] Medical Department II, J.-W.-Goethe University Hospital Frankfurt, Germany

[7] Medical Department V, Heidelberg University Hospital, Germany

[8] Department of Hematology, Essen University Hospital, Germany

[9] Medical Department 5, University Hospital of Paracelsus Medical University Nuremberg, Germany

[10] Department of Medicine 5, Uniklinikum Erlangen, Germany

[11] Department for Internal Medicine III, Klinikum Chemnitz, Germany

[12] Medical Department II, University Hospital Würzburg, Germany

[13] Department of Oncology, Hematology, Hemostaseology and Stem Cell Transplantation, University Hospital RWTH Aachen, Aachen, Germany & Center for Integrated Oncology (CIO), Aachen, Bonn, Cologne, Düsseldorf (ABCD), Aachen, Germany

[14] Klinik für Innere Medizin II, Jena University Hospital, Jena, Germany

[15] Department of Internal Medicine, Hematology, Oncology and Immunology, University Hospital Marburg, Germany

[16] Department of Hematology, Oncology and Palliative Medicine, Robert-Bosch-Hospital Stuttgart, Germany

[17] Internal Medicine, Hematology/Oncology, Palliative Medicine, Gemeinschaftsklinikum Mittelrhein, Koblenz, Germany

[18] Department for Hematology, Oncology and Palliative Medicine, Rems-Murr-Klinikum, Winnenden, Germany

[19] Department for Internal Medicine III, Helios Dr Schmidt Hospital Wiesbaden, Germany

[20] Department for Oncology and Hematology, Klinikum Bayreuth, and Comprehensive Cancer Center Erlangen-EMN, Germany

[21] Department for Hematology, Oncology and Palliative Medicine, Klinikum Bielefeld, Bielefeld, Germany

[22] Medical Department II, St. Bernward Hospital, Hildesheim, Germany

[23] Medical Department II, Hematology and Oncology, DIAKO Bremen, Germany

[24] Department for Internal Medicine IV, University Hospital Halle (Saale), Germany

[25] Medical Department I, Hematology and Cell Therapy, University Hospital Leipzig, Germany

[#] ***Corresponding author:*** David Baden, Department of Hematology and Oncology, University Hospital Schleswig-Holstein, Christian-Albrechts-University, 24105 Kiel, Germany; david.baden@uksh.de, phone +49-431-50062443, fax +49-431-50022504

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Key Point:

- No difference in overall survival was noted between early and delayed treatment initiation with venetoclax-based combination therapy in patients with newly diagnosed AML in two independent cohorts

Abstract

In newly diagnosed acute myeloid leukemia, immediate initiation of treatment is standard of care. However, deferral of antileukemic therapy may be indicated to assess comorbidities or pre-therapeutic risk factors. We explored the impact of time from diagnosis to treatment on outcomes in newly diagnosed acute myeloid leukemia undergoing venetoclax-based therapy in two distinct cohorts.

By querying the Study Alliance Leukemia database and the global health network TriNetX, we identified 138 and 717 patients respectively with an average age of 76 and 72 years who received venetoclax-based first-line therapy. When comparing patients who started treatment earlier or later than 10 days after initial diagnosis, no significant difference in median overall survival was observed - neither in the SAL cohort (7.7 vs. 9.6 months, p=.42) nor in the TriNetX cohort (7.5 vs. 7.2 months, p=.41). Similarly, severe infections, bleeding, and thromboembolic events were equally observed between early and later treatments, both in the overall patient groups and specific subgroups (age ≥75 years or leukocytes ≥20x10^9/L).

This retrospective analysis indicates that delaying the start of venetoclax-based therapy in newly diagnosed acute myeloid leukemia might be a safe option for selected patients, provided that close clinical monitoring is performed.

Introduction

The diagnosis of acute myeloid leukemia (AML) is deemed a medical emergency, given that untreated cases result in dismal outcomes [1]. Immediate initiation of treatment has therefore been the standard of care for newly diagnosed patients with AML since the early days of leukemia therapy [2]. Deferral of treatment was an exception and may only have occurred when assessment or treatment of comorbidities was necessary. Researchers have confirmed the paradigm of immediate treatment initiation when in 2009 Sekeres et al. showed that response rates and overall survival worsened if a treatment delay of more than 5 days occurred in patients under the age of 60 years [3]. However, as more and more targeted treatment approaches become available, deferral of treatment in newly diagnosed AML may be indicated to treat according to molecular analysis [4–7]. A study conducted in 2013 showed comparable treatment outcomes in patients with curative intent receiving intensive chemotherapy even when treatment is postponed [8]. Likewise, in a comprehensive analysis published by the Study Alliance Leukemia (SAL) in 2020 involving 2263 patients undergoing intensive chemotherapy induction, no disparity in overall survival or other clinical outcomes was observed based on the initiation of treatment [9]. Conversely, a separate Swedish study with 2374 patients and a study from the National Cancer Database of the United States with 55985 patients noted a survival impact with treatment delays [10,11]. However, results of these population-based studies may be dominated by selection of induction regimens and their relapse rates rather than by treatment delay. It is noteworthy that patients who underwent early treatment were skewed towards a younger age. A meta-analysis conducted in 2023 including these studies and others but excluding the extensive United States study, found a correlation between prolonged time from diagnosis to treatment initiation (TDT) and a decreased likelihood of achieving complete remission (CR) [12]. Overall, the described differences in these studies were marginal and the clinical relevance of these results may be limited. We argue that the prognosis of younger or fit patients is only minimally affected, if at all, by the TDT. But as all available data was derived exclusively from AML patients who are eligible for intensive chemotherapy, we sought to expand this clinical question to elderly patients unfit for intensive therapy.

The approval of venetoclax in combination with hypomethylating agents (HMA) in newly diagnosed AML in 2018 by the FDA represented a significant advance in AML therapy, offering improved outcomes for elderly or frail patients not eligible for intensive chemotherapy. Although there are subtype-specific differences in the antileukemic efficacy of venetoclax, venetoclax-based therapies are indicated regardless of WHO/ELN/ICC classification [13]. With the advent of targeted therapies, there are new opportunities to address genetic alterations in AML also in patients ineligible for intensive treatment, and thus increase the number of treatment options [14,15]. Since a comprehensive genetic diagnosis or addressing pre-existing conditions and associated complications can take more than 7-10 days, we asked whether a prolonged TDT with venetoclax-based therapies impairs outcome in patients with newly diagnosed AML.

Methods

This study used real-world data from two independent cohorts to compare TDT in AML: The patient registry of the SAL and electronic health records (EHR) from TriNetX, LLC ("TriNetX"), a global federated health research network. Patients from both cohorts were stratified into two treatment groups: those treated within the first 9 days (TDT 0-9) and those treated from day 10 onwards (TDT ≥10). The SAL-trial was conducted in accordance with the principles of the Declaration of Helsinki and the protocol has been approved by the ethics committees of all participating centers. The study is registered under the ClinicalTrials.gov ID NCT03188874. TriNetX utilizes aggregated de-identified patient records, therefore no ethics committee approval was required.

SAL-registry query design

The SAL Registry captures cases of adult AML, examining laboratory values, genomics, survival, and relapse for academic and clinical insights. We selected patients with newly diagnosed AML treated with venetoclax in combination with HMA or low-dose Cytarabine (LDAC) between January 1st, 2018, and April 15th, 2023. Only patients with a follow-up of at least 6 months or death within this period were included. Data query was performed on November 28th, 2023. To enhance data validity and specificity, patients receiving

treatment >50 days after diagnosis were excluded from the analysis. Patient characteristics were analysed using descriptive statistical methods. The binary outcomes CR or complete remission with incomplete count recovery (CRi), early death (ED) and allocation to allogeneic hematopoietic stem cell transplant (HSCT) were expressed as a percentage and compared using the χ^2-test, while for overall survival (OS), event-free survival (EFS) and relapse-free survival (RFS) the Kaplan-Meier approach was used. EFS was defined as either primary treatment failure or relapse or death, RFS was calculated from the time of CR/CRi until relapse or death.

TriNetX query design

TriNetX is a healthcare network that facilitates access to EHR from currently more than 250 million patients worldwide providing data for clinical and retrospective studies [16]. We searched for patients from the TriNetX database who were treated with newly diagnosed AML between January 1st, 2015, and July 1st, 2023, and met the following criteria: Venetoclax treatment in combination with HMA or LDAC, follow-up of at least 1 year or death, no prior treatment of anthracycline/mitoxantrone or venetoclax before diagnosis of AML, no prior diagnosis of AML, age ≥20 years, no intensive therapy within the first 8 weeks after diagnosis and no prior HSCT. Data query on the platform was performed on October 24th, 2023. Analyses were done utilizing the statistical tools provided within the TriNetX network, as only aggregated data was accessible. The baseline characteristics age and body mass index (BMI) were therefore described by means and standard deviations (SD), while the other continuous variables were described by median and interquartile range (IQR). Age and BMI were compared using student's t-test, dichotomous variables by the χ^2-test. As no statistical analyses for aggregated data other than the student's t-test are available on the platform, no comparison could be made for median and IQR. Further details are described in the supplement.

Results

We identified a total of 855 patients (717 TriNetX, 138 SAL registry) who received first-line treatment of AML with venetoclax based regimens. The patient selection process is illustrated as CONSORT flow diagram (Figure S1).

SAL-registry

At data cut-off, a total of 8681 newly diagnosed AML patients were registered in the SAL registry, of whom 138 received venetoclax in combination with HMA or LDAC as first line treatment and met inclusion criteria for this analysis. Of these patients, 103 received treatment within the first 9 days after diagnosis (75%, TDT 0-9), while 35 patients were treated on day 10 or later (25%, TDT ≥10) (Table 1). Median TDT was 4 days (IQR 2-6 days) in the TDT 0-9 group and 15 days (IQR 12-21 days) in the TDT ≥10 group, respectively (Figure S2). With a median age of 77 years (range, 58-89 years), patients in the TDT 0-9 group were significantly older than in the TDT ≥10 group (median age 73 years, range, 29-86 years; p=0.007). We observed no significant difference in hemoglobin levels (8.1 g/dl vs. 8.6 g/dl, p=.49), platelet counts ($38x10^{12}$/L vs. $57x10^{12}$/L, p=.14), percentage of bone marrow blasts (60% vs 45%, p=.07) or lactate dehydrogenase (LDH) (396 U/L vs. 302 U/L, p=.45). The percentage of patients with leukocytosis defined as white blood cell count (WBC) ≥$20x10^{9}$/L was similar (34% vs. 20%, p=.12). According to the ELN2017 risk stratification, favourable, intermediate, and unfavourable genetic risks were present in 15%, 30% and 55% of patients, respectively. Patients with favourable genetic risks were only identified in the TDT 0-9 group; however, this difference was not statistically significant. Comorbidities were present to the same extent in both cohorts (91% vs. 94%, p=.57). CR or CRi was achieved in 43 of 103 (42%) and 16 of 35 (46%) patients, respectively. The median OS was 6.7 months with a median follow-up time of 16 months in the TDT 0-9 and 12 months in the TDT ≥10 group (Table 2). HSCT was realised in 10 of 138 patients (7%). To determine whether very early treatment provides a survival benefit, we divided the TDT 0-9 group along the median into a TDT 0-4 and a TDT 5-9 subgroup. No differences in OS were observed (median survival 6.1 vs 9.5 months, p=.2).

With an OS of 7.7 (95%CI 5.3, 12) vs. 9.6 (95%CI 6.4, -) months, there was only a small, statistically non-significant difference between the TDT 0-9 and TDT ≥10 groups (p=.42) (Figure 1a). Likewise, a numerical

but not statistically significant difference was observed for RFS or EFS (36 vs 14 months, p=.33 and 6.2 vs. 5.5 months, p=.93; Figure S3). RFS at 12 months was 57% (95%CI 42%, 78%) and 55% (95%CI 32%, 96%), median EFS at 12 months was 37% (95%CI 29%, 48%) and 38% (95%CI 25%, 59%). The OS in subgroups of individuals aged ≥75 years (8.4 vs. 21 months, p=.62) or with WBC ≥20x10^9/L (9.1 vs. 12 months, p=.80) displayed no statistically significant differences between early and late treatment. The OS after 12 months was 42% (95%CI 31%, 58%) and 52% (95%CI 30%, 88%) in the patients aged ≥75 years and 46% (95%CI 31%, 67%) and 38% (95%CI 14%, 100%) in the WBC ≥20x10^9/L subgroup (Table 2, Figure S4). Early death after 30 days occurred in 14 of 138 (10%) patients with no significant difference between the groups (11% vs. 9%, p=.72). Hydroxyurea administration lacked consistent documentation and thus is not included in the analysis.

TriNetX-cohort

At the time of analysis, there were 32058 patients with newly diagnosed AML in the TriNetX EHR library. Of these, 717 AML patients with sufficient documentation were identified who received combination treatment with venetoclax and met the inclusion criteria. Among them, 491 patients received treatment within the first 9 days after diagnosis (68%, TDT 0-9), while in 226 patients, treatment was initiated on day 10 or later (32%, TDT ≥10). The patient population comprised 80% Whites, 6% African Americans, 2% Asians and 12% other US-citizens of unknown ethnicity from 41 U.S.-based healthcare organizations.

Mean age was 71.8 ± 8.9 years, with very little variance between both groups (Table 3). We observed more patients with a WBC ≥20x10^9/L in the TDT 0-9 group (36% vs 18%, p<.0001) compared to TDT ≥10. Regarding sex or comorbidities, no significant differences between the two groups were present. Median TDT was 3 days (IQR 1-5 days) in the TDT 0-9 group and 17 days (IQR 13-25) in the TDT ≥10 group, respectively (Figure S2). Median follow-up, defined as time from diagnosis to last documented visit or death was 11.0 months.

Median OS was 7.5 months in the TDT 0-9 group and 7.2 months in the TDT ≥10 group (p=.41, Table 4, Figure 1b). This parity persisted even after using PSM to match patients for WBC and age, effectively

controlling for the increased prevalence of leukocytosis in the TDT 0-9 group (7.4 vs. 7.2 months, p=.49). Balanced across the two groups, 37 of 717 patients (5%) received HSCT for consolidation.

When we queried for adverse events by selected ICD codes (Table S1) no differences between TDT 0-9 and TDT ≥10 were identified. Severe infections occurred in 244 of 717 patients (34%). We found acute kidney injury in 154 of 717 patients (21%) again without significant association to TDT (Table 5). We noted a higher 30-day death rate in the TDT 0-9 group (19%) compared to the TDT ≥10 group (10%, p=.005). The difference was not present after matching patients for WBC and age or if 60-day early mortality was analysed (Table 4). Subgroup analyses revealed no differences in overall survival between the TDT 0-9 vs TDT ≥10 group in patients ≥75 years old (7.9 vs. 7.2 months, p=.86), with WBC ≥20x10^9/L (4.0 vs. 4.0 months, p=.31) or any vs. no comorbidities (7.9 vs. 6.7 months, p=.26) (Figure S5-S7). We observed no significant differences in clinical outcomes of these subgroups such as severe infections, renal failure, heart or liver failure, bleeding, or thromboembolic events either (Table S2-S4). As with the SAL-cohort, we divided the TDT 0-9 group along the median into a TDT 0-3 and a TDT 4-9 subgroup. Again, no differences in OS or other clinical outcomes were observed (median survival 6.9 vs 7.9 months, p=.32). During the initial 30 days post-diagnosis, hydroxyurea was prescribed to 32% of TDT 0-9 group patients, and 13% in the TDT ≥10 group (p<.001). In patients with leukocytosis, hydroxyurea was administered in 77% in the TDT 0-9 group and in 54% in the TDT ≥10 group (p=.006).

Discussion

We examined for the first time the effect of TDT on clinical outcomes in newly diagnosed AML patients treated with venetoclax-based regimens. Both SAL and TriNetX patient cohorts were overall well balanced according to clinical parameters and patient demographics, which was mostly maintained upon stratification into short and long TDT. Although the median age was higher in the SAL TDT 0-9 group, the proportion of patients aged ≥75 years was similar across both SAL TDT groups. In the TriNetX cohort, no relevant age difference was observed, suggesting that the age disparity in the SAL cohort between TDT 0-9 and TDT ≥10 groups may be attributed to the relatively small sample size. In the SAL cohort, TDT 0-9 displayed a trend for improved RFS and EFS, with slightly shorter OS compared to the TDT ≥10 group. This observation is likely caused by a few cases with late events and again a consequence of the small sample size, impacting RFS and EFS but not OS. In the TriNetX cohort, no significant differences in OS were observed between the TDT groups, neither in the primary cohort nor in the respective subgroups.

The greater proportion of patients with leukocytosis (WBC ≥20x10^9/L) in the TDT 0-9 group compared to the TDT ≥10 group in the TriNetX cohort may reflect a consensus among treating physicians not to delay treatment initiation in AML with high cell turnover. In the SAL cohort, the proportion of patients with leukocytosis (WBC ≥20x10^9/L) did not differ between the TDT 0-9 and TDT ≥10 groups, again probably due to the lower number of patients in this cohort. As repeated WBC counts were not available for analysis, information on leukocyte dynamics was lacking. In the TriNetX cohort, overlapping survival curves suggest potential unaddressed non-proportional hazards, likely caused by sample size limitations. However, the overall lack of outcome differences in patients with WBC ≥20x10^9/L suggests that carefully selected individuals may tolerate elevated WBCs for a few days, possibly with additional hydroxyurea treatment.

The absence of disparities in survival or other clinically significant outcomes, such as severe infections, hemorrhage, or organ failure between TDT 0-9 and TDT ≥10 groups in both the SAL and TriNetX cohorts indicates that delaying treatment does not seem to pose an elevated risk for older patients and those with comorbidities. Consistent signals of equivalence in two international cohorts imply widespread success in clinically managing patients with delayed TDT, likely reflecting good clinical practice across different

regions. At the same time, the antileukemic effect of venetoclax does not appear to be affected by treatment delay. Therefore, unfavourable outcomes in unfit AML patients treated with venetoclax are likely attributed to factors beyond TDT.

We found a higher early mortality (assessed *after* start of treatment) in the TDT 0-9 group compared to the TDT ≥10 group of the TriNetX cohort. To account for the impact of older age and high WBC as significant factors in early mortality, we employed PSM to match the TriNetX groups based on these variables [17–19]. No statistically significant difference in early mortality was observed after the use of PSM. Furthermore, there were no discernible differences in specific clinical outcomes or treatment-related complications that would implicate antileukemic treatment as a significant factor in 30-day early mortality. Consequently, we conclude that TDT had no effect on early mortality.

Comparable to several other real-world analyses, we observed lower remission rates and OS (6.7 to 7.4 months) and a higher early death rate (10 to 16%) in both patient cohorts compared to the venetoclax pivotal study 'VIALE-A' (median OS 14.7 months, early death rate 7%) [13]. VIALE-A targeted an elderly and frail patient population, using specific inclusion and exclusion criteria to characterise the study population. These criteria are presumably applied less strictly in practice, which broadens the indication (e.g. patients with advanced kidney, liver or heart problems, chronic lung disease or advanced diabetes). Consequently, our data is in line with reported median overall survival rates of between 9 and 13 months in several real-world analyses and a meta-analysis including 1134 patients that showed a pooled median survival time of 9.4 months [20–24]. Outside of prospective, controlled, randomised clinical trials (RCTs), it is suspected that reduced safety monitoring and bone marrow assessments as well as decreased treatment adherence may contribute to impaired prognosis as well as distortion of efficacy parameters, such as response rates, and RFS [20–23,25]. While an RCT may be more useful to estimate true clinical potential of a therapeutic regimen, real-world-analyses such as our report are required to assess clinical questions for which a RCT will likely never emerge. One such clinical issue is the optimal timing of treatment initiation in patients with newly diagnosed AML.

Like all analyses based on real-world data, there are several limitations to consider. While we made efforts to accommodate known risk factors, non-randomized data inherently cannot be adjusted for unknown risk factors. For example, our results suggest that patients with evidence of rapid proliferation were treated earlier. However, there is little information on other patient or disease characteristics that may have influenced physicians' decision to start treatment at a particular time. We cannot account for instances where patients scheduled for intensive treatment received venetoclax-based therapy or vice versa, as this information is not documented in the EHR or the SAL registry. Furthermore, both SAL and TriNetX cohorts exhibit selection bias and EHR may include misdiagnoses and lack information on potential confounders. The TriNetX cohort faces sampling bias due to non-random selection, missing individuals with limited healthcare access or patients receiving treatment outside facilities of the network. We lack information on facility size, which could affect molecular diagnostics waiting times and resource limitations for severe complications. Similar to other analyses conducted on TDT, the retrospective nature of this analysis fails to account for patients that succumb to leukemia before treatment initiation [3,8–12]. But as untreated AML leads to a dismal outcome, a general assumption can be made: Patients untreated for an extended period after diagnosis encounter a higher before-treatment mortality rate compared to those promptly treated. However, by focusing on time from diagnosis to *treatment*, the analysis addresses the question whether patients receiving treatment after a specific timeframe have the same benefits from this therapy as patients who are treated immediately. Based on our results, we conclude that a delay in treatment does not result in an accumulation of risk factors or diminishes therapy efficacy and, consequently, does not influence outcome.

In summary, our results show for the first time that TDT has no clinically relevant impact on OS in patients with newly diagnosed AML treated with venetoclax-based regimen as first line therapy. Furthermore, we found no differences in terms of treatment safety, EFS or RFS. Therefore, we assume that the antileukemic activity of venetoclax-based therapies is independent of the TDT. While our data do not suggest an imperative for extensive genetic testing prior to initiating AML therapy, delaying treatment, when clinically

suitable and promising, may enhance outcomes for selected patients, e.g. those harbouring targetable lesions and reversible comorbidities.

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Table 1: Patient characteristics SAL-Registry

	TDT 0-9 days	TDT ≥10 days	All	p-value°
Total number, n (%)	103	35	138	
Patient characteristics				
Age, years (Median, Range)	77 (58-89)	73 (29-86)	76 (29-89)	**.007**
Male, n (%)	56 (54)	22 (63)	78 (57)	.38
Female, n (%)	47 (46)	13 (37)	60 (43)	.38
Age ≥75 years, n (%)	57 (55)	16 (46)	73 (53)	.32
WBC ≥20x10^9/L, n (%)	35 (34)	7 (20)	42 (30)	.12
Comorbidities, n (%)	94 (91)	33 (94)	127 (92)	.57
BMI, kg/m² (Median, Range)	26 (18-39)	26 (19-43)	26 (18-39)	.52
ECOG				.04
0-1	63 (66)	29 (85)	92 (71)	
2-4	32 (34)	5 (15)	37 (29)	
missing	8	1	9	
Lab. parameters (Median, Range)				
WBC (x10^9/L)	6.1 (0.1-139)	2.6 (0.1-190)	4.9 (0.1-190)	0.47
Hemoglobin (g/dl)	8.1 (3.9-14.8)	8.6 (5.7-12.9)	8.2 (3.9-14.8)	0.49
Platelets (x10^{12}/L)	38 (0.1-509)	57 (0.1-245)	40 (0.1-509)	0.14
LDH (U/L)	396 (108-3140)	302 (133-3500)	378 (108-3500)	0.45
Bone marrow blasts (%)	60 (8-99)	45 (12-95)	58 (8-99)	0.07
AML Characteristics (n, %)				
ELN2017[#]				0.10
favorable	15 (19)	0 (0)	15 (15)	
intermediate	22 (28)	8 (40)	30 (30)	
adverse	42 (53)	12 (60)	54 (55)	
missing	24	15	39	
AML-type				0.31
De novo	93 (90)	32 (91)	125 (91)	
sAML	5 (5)	3 (9)	8 (6)	
tAML	5 (5)	0 (0)	5 (3)	

°Bonferroni-correction was used to adjust for multiple testing (p <.0071 for significance). [#]Information available for 99 patients (72%). *Abbreviations: TDT:* time from diagnosis to treatment, *WBC:* white blood cell count, *BMI:* body mass index, *ECOG:* Eastern Cooperative Oncology Group, *LDH:* Lactate dehydrogenase, *ELN2017:* European Leukemia Net 2017 risk stratification for AML, *sAML:* secondary acute myeloid leukemia, *tAML:* therapy-related acute myeloid leukemia

Table 2: Treatment outcomes SAL-Registry

	TDT 0-9 days	TDT ≥10 days	All	p-value
Median OS, months (95% CI)	7.7 (5.3, 12)	9.6 (6.4, -)	6.7	.42
Age ≥75 years	8.4 (5.0, -)	21 (3.3, -)	9.1	.62
WBC ≥20x10^9/L	9.1 (5.8, -)	12 (2.4, -)	9.5	.80
CR/CRi, n (%)	43 (42)	16 (46)	59 (43)	.68
EFS, months (95% CI)	6.2 (4.3, 9.4)	5.5 (2.9, -)	5.9	.93
RFS, months (95% CI)	36 (11, -)	14 (7.2, -)	7.2	.33
Early death				
30d, n (%)	11 (11)	3 (9)	14 (10)	.72
60d, n (%)	22 (21)	6 (17)	28 (20)	.59
HSCT, n (%)	8 (8)	2 (6)	10 (7)	.69

Abbreviations: TDT: time from diagnosis to treatment, *OS:* overall survival, *WBC:* white blood cell count, *CR/CRi:* complete remission/ complete remission with incomplete count recovery, *EFS:* event-free survival, *RFS:* relapse-free survival, *HSCT:* allogeneic hematopoietic stem cell transplant

Table 3: Patient characteristics TriNetX

	TDT 0-9 days	TDT ≥10 days	All	p-value°
Total number, n (%)	494 (69)	223 (31)	717	
Patient characteristics				
Age, years (Mean ±SD)	71.7 ± 8.4	71.9 ± 9.8	71.8 ± 8.9	.81
Male, n (%)	275 (55)	130 (58)	405 (56)	.51
Female, n (%)	218 (45)	92 (42)	310 (44)	.51
Age ≥75 years, n (%)	198 (40)	106 (47)	304 (42)	.06
WBC ≥20x10^9/L, n (%)	162 (33)	35 (16)	217 (30)	**<.0001**
Comorbidities, n (%)	323 (65)	152 (68)	475 (66)	.46
BMI, kg/m² (Mean ±SD)	29.1 ± 6.5	27.1 ± 6.6	28.5 ± 6.6	.03
Lab. parameters (Median, IQR)				
WBC (x10^9/L)	6.4 (1.9-29.6)	3.2 (1.4-7.7)	4.6 (1.9-24.9)	
Hemoglobin (g/dl)	8.3 (7.6-9.4)	8.5 ± (7.7-9.7)	8.3 (7.6-9.5)	
Platelets (x10^{12}/L)	47 (26-89)	53 (27-114)	51 (25-97)	
LDH (U/L)	356 (226-620)	264 (184-554)	329 (210-614)	
Bilirubin (mg/dl)	0.6 (0.5-0.9)	0.6 (0.4-1.0)	0.6 (0.5-0.9)	
Creatinine (mg/dl)	0.98 (0.79-1.31)	0.92 (0.78-1.21)	0.97 (0.79-1.29)	
Albumin (g/dl)	3.4 (3.0-3.9)	3.6 (3.2-4.1)	3.5 (3.0-3.9)	
CRP (mg/L) *	40 (9-100)	52 (10-108)	42 ± (9-118)	

°Bonferroni-correction was used to adjust for multiple testing; p <.00625 for significance; * value available for less than 30% of patients at first diagnosis. *Abbreviations: TDT:* time from diagnosis to treatment, *WBC:* white blood cell count, *BMI:* body mass index, *LDH:* Lactate dehydrogenase, *CRP:* C-reactive protein

Table 4: Overall survival and early death TriNetX

	TDT 0-9 days	TDT ≥10 days	All	p-value°
Median OS, months (95% CI)				
Overall	7.5 (5.8, 8.6)	7.2 (5.5, 7.9)	7.4 (5.8, 7.9)	.41
after PSM	7.4 (5.3, 9.6)	7.2 (4.6, 8.1)	-	.49
Age ≥75 years	7.9 (5.5, 9.1)	7.2 (4.1, 8.6)	7.4 (5.6, 8.3)	.86
WBC ≥20x10^9/L	4.0 (2.5, 5.7)	4.0 (2.1, 5.6)	4.5 (2.9, 5.6)	.31
Comorbidities	7.9 (5.8, 9.7)	6.7 (4.3, 8.1)	7.6 (6.0, 8.7)	.26
3-year survival probability (%)				
Overall	20.5	17.6	19.5	
after PSM	16.2	16.9	-	
Age ≥75 years	14.9	22.1	16.5	
WBC ≥20x10^9/L	17.6	5.7	14.0	
Comorbidities	20.2	16.6	18.7	
#Early death 30d (n, %)	92 (18.6)	23 (10.4)	115 (16.0)	**.005**
after PSM	25 (11.5)	23 (10.6)	-	.75
#Early death 60d (n, %)	134 (27.2)	62 (27.9)	196 (27.3)	.91
after PSM	45 (20.7)	60 (27.7)	-	.11
HSCT	25 (5.1)	12 (5.4)	37 (5.2)	.86

°Bonferroni-correction was used to adjust for multiple testing (p <.008 for significance), Log-Rank-Test; #calculated from start of treatment. *Abbreviations: TDT:* time from diagnosis to treatment, *OS:* overall survival, *PSM:* Propensity score matching, *WBC:* white blood cell count, *CR/CRi:* complete remission/ complete remission with incomplete count recovery, *EFS:* event-free survival, *RFS:* relapse-free survival, *HSCT:* allogeneic hematopoietic stem cell transplant

Table 5: Rates of adverse events across the TriNetX cohort stratified according to TDT. Patients with outcome event prior to first diagnosis of AML were excluded.

Event (n, %)	TDT 0-9 days	TDT ≥10 days	Odds ratio	95% CI	p-value
Severe infection	159, 37.0	85, 42.7	0.79	0.56-1.11	.18
Renal failure	97, 33.3	57, 33.3	1.00	0.67-1.49	.78
[#]Dialysis	[#]10, 2.02	[#]10, 4.48	-	-	-
Liver failure	20, 4.12	10, 4.48	0.92	0.42-1.99	.73
Heart failure	41, 9.05	28, 13.2	0.66	0.39-1.09	.17
Bleeding	109, 28.0	39, 22.9	1.31	0.87-1.99	.21
Thrombosis	83, 20.3	33, 17.7	1.18	0.86-1.99	.64

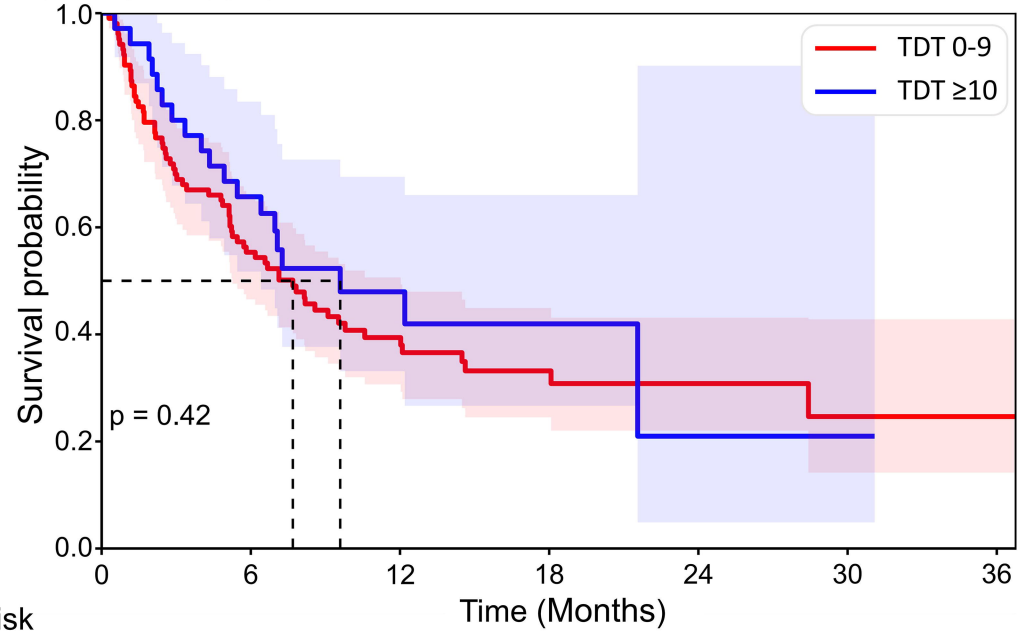
[#] censored, less than 10 patients. *Abbreviations: TDT:* time from diagnosis to treatment, *CI:* confidence interval

Figure Legend

Figure 1. Overall survival of patients in the SAL- and TriNetX cohort

(A) Overall survival of patients in the SAL-cohort calculated from diagnosis of AML. Median OS was 7.7 (95% CI 5.3, 12) months in the TDT 0-9 and 9.6 (95% CI 6.4, -) months in the TDT ≥10 group (p=.42). Median follow-up time was 16 and 12 months, respectively. **(B)** Overall survival of patients in the TriNetX-cohort calculated from diagnosis of AML. Median OS was 7.5 (95% CI 5.8, 8.6) months in the TDT 0-9 group and 7.2 (95% CI 5.5, 7.9) months in the TDT ≥10 group (p=.41). Median follow-up time was 11 months in the whole cohort. *Abbreviations: TDT:* time from diagnosis to treatment, *CI:* confidence interval, *SAL:* Study Alliance Leukemia

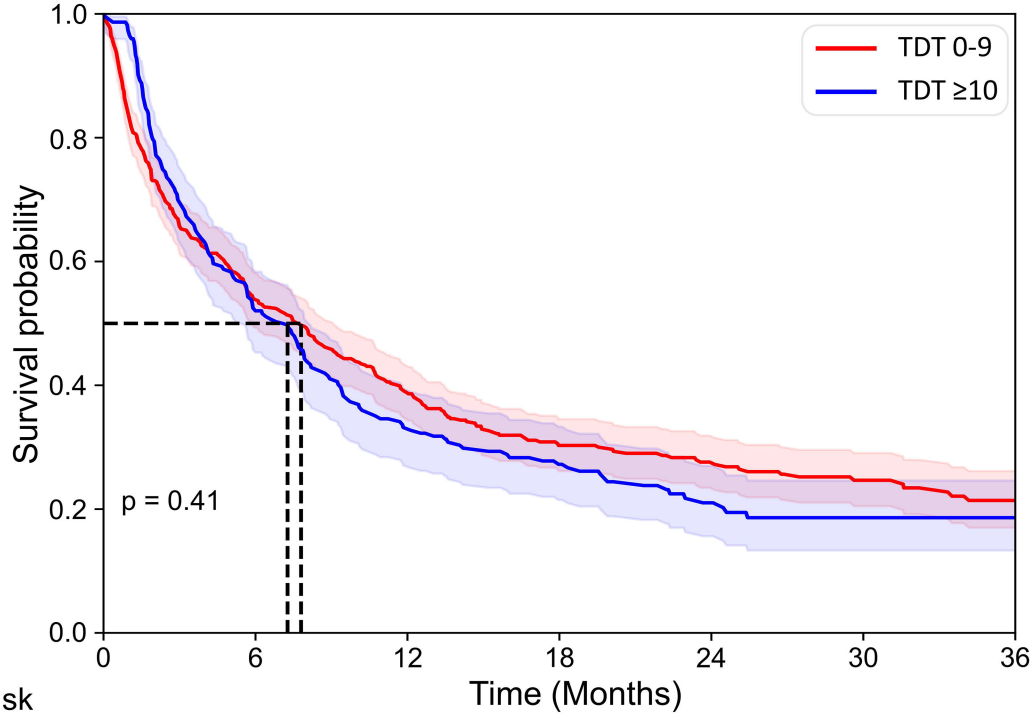
A: Overall Survival in SAL-cohort



Number at risk

Time (Months)	0	6	12	18	24	30	36
TDT 0-9	103	57	28	14	9	2	2
TDT ≥10	35	23	8	3	1	1	0

B: Overall Survival in TriNetX-cohort



Number at risk

Time (Months)	0	6	12	18	24	30	36
TDT 0-9	494	261	185	97	74	41	31
TDT ≥10	223	116	72	50	28	22	22

Time from diagnosis to treatment has no impact on survival in newly diagnosed acute myeloid leukemia treated with venetoclax-based regimens - Supplement

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Supplementary information on ethics and study design

Regarding the TriNetX network, all data collection, processing, and transfers were conducted in compliance with data privacy laws applicable to the participating healthcare organizations, including EU Data Protection Regulation 2016/679, the General Data Protection Regulation on the protection of individuals regarding the processing of personal data, and the Health Insurance Portability and Accountability Act ("HIPAA"), the U.S. federal health information privacy and security law. Analyses are performed on anonymised or pseudonymised/de-identified (in accordance with HIPAA) data housed at the healthcare organisations, with only aggregated results returned to the TriNetX platform and users. Because this study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, this study was exempted from Institutional Review Board approval. Patients from both cohorts were stratified into two treatment groups: those treated within the first 9 days (TDT 0-9) and those treated from day 10 onwards (TDT ≥10). The cut-off was chosen based on the anticipated global accessibility of molecular test results. After 10 days, these results are expected to be readily available in the majority of cases, extending beyond academic research centres in Europe and North America [1].
The term mortality when used with a percentage means death rate per patient sample.

Statistical analysis TriNetX-cohort
The ICD and procedure codes used for analyses are listed in the Supplement Table 1. To improve the validity of data and account for potential documentation errors, we excluded patients from analysis who received treatment >50 days after diagnosis. Patients were assigned to the respective clinical characteristics (e.g., comorbidities) or outcomes if one or more of the listed ICD or procedure codes were listed in the EHR before the initial diagnosis or after the initial diagnosis of AML, whichever was applicable. As no statistical analyses for aggregated data other than the student's t-test are available on the platform, no comparison could be made for median and IQR. Since white blood cell counts (WBC) have a known impact on prognosis, we divided the patients into groups with high versus low leukocyte counts using a cut-off of $20x10^9$/L and compared these as a categorical variable [2]. The threshold value of $20x10^9$/L was chosen to differentiate patients in whom cytoreductive therapy, for example with hydroxyurea, was likely before starting venetoclax-based therapy. Survival calculated according to the Kaplan-Meier method was measured either from the time of diagnosis or, in the case of the analysis of early deaths, from the start of treatment. We applied Propensity Score Matching (PSM) to match patients for age and WBC and create comparable cohorts. The median follow-up time was calculated as the time from diagnosis to the last documented visit or death, whichever occurred first. For analysis of clinical outcomes and complications, patients with events prior to the first diagnosis of AML were excluded. To account for multiple testing, we applied the Bonferroni correction. The respective p-values are given.

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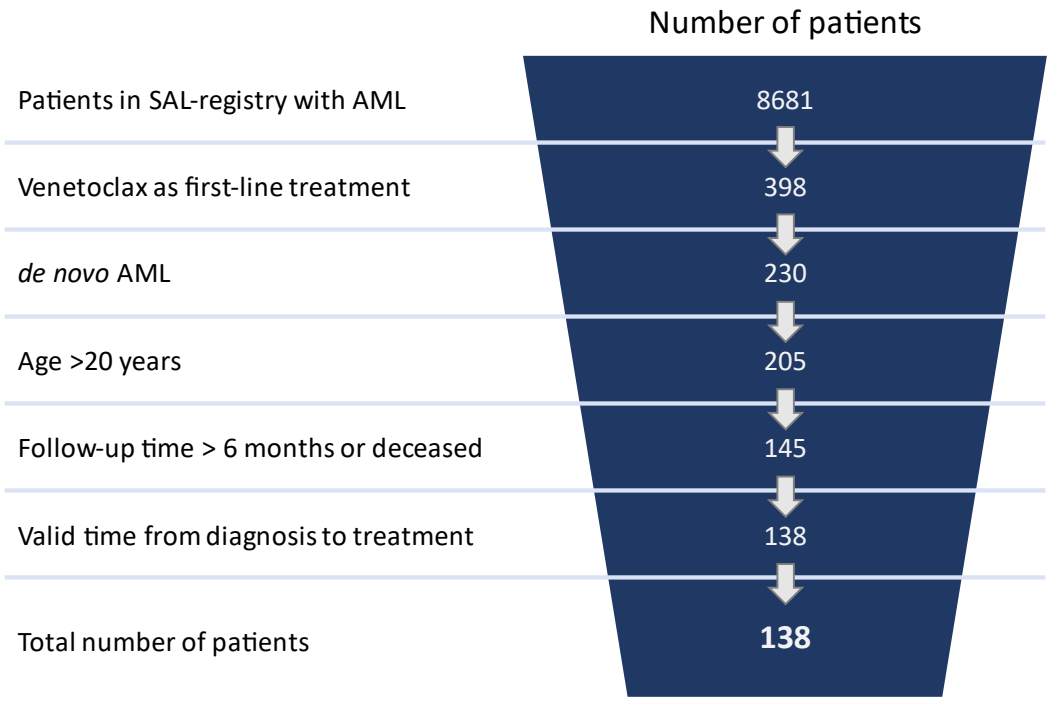
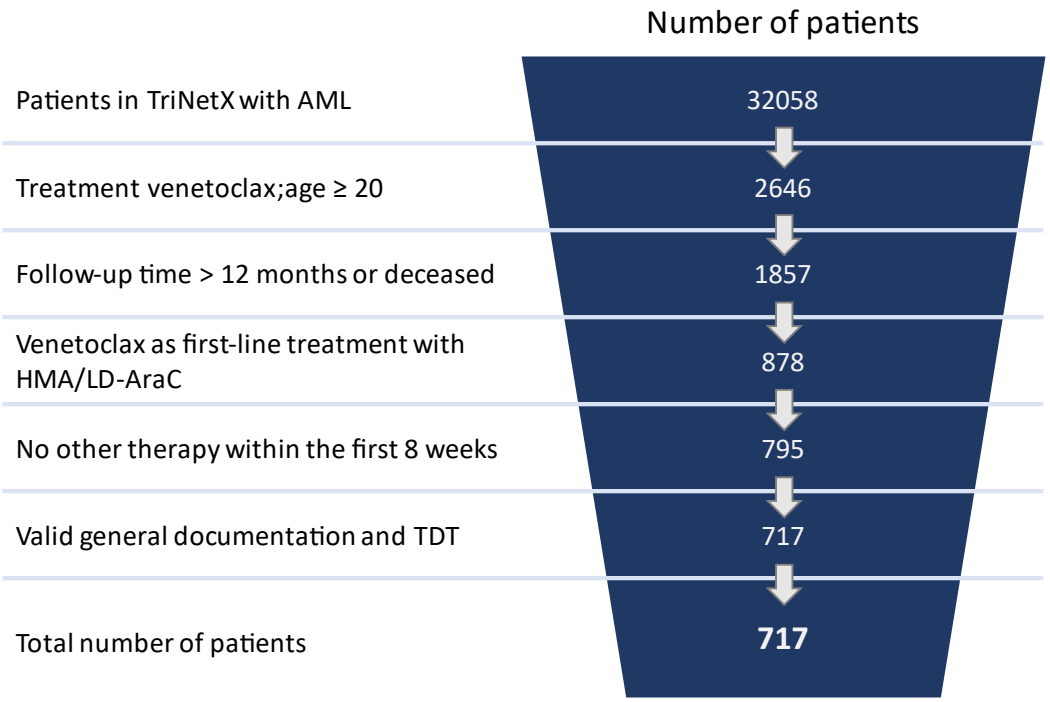
Supplement Figure 1a: Patient selection SAL



Supplement Figure 1b: Patient selection TriNetX

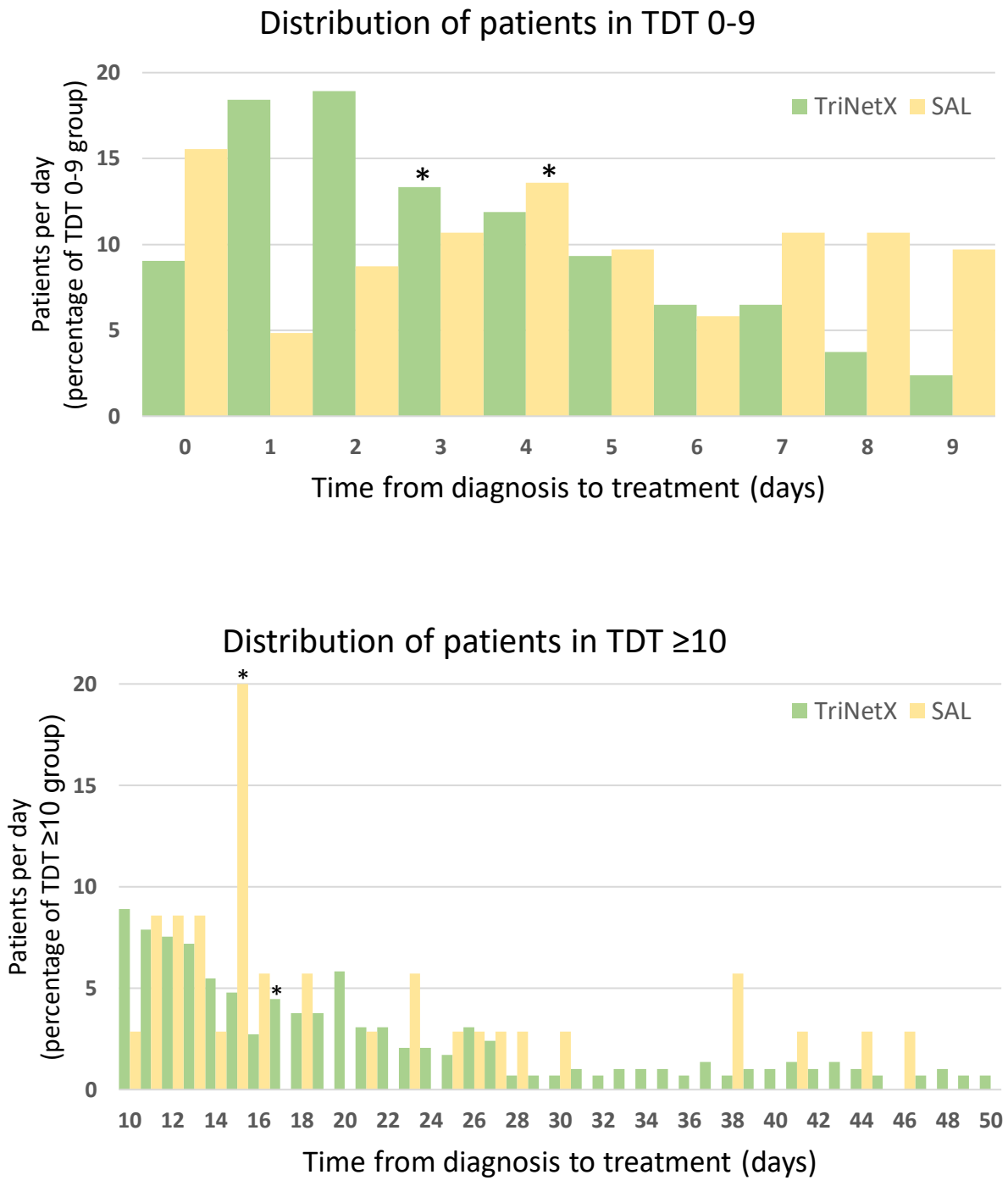


Supplement Table 1: List of ICD-10-CM and procedural codes used for TriNetX and SAL

Group	ICD-10-CM / procedure	Disease
AML	C92.0	Acute myeloblastic leukemia
AML	C92.5	Acute myelomonocytic leukemia
AML	C92.6	Acute myeloid leukemia with 11q23-abnormality
AML	C92.A	Acute myeloid leukemia with multilineage dysplasia
AML	C92.9	Myeloid leukemia, unspecified
AML	C93.0	Acute monoblastic/monocytic leukemia
AML	C93.9	Monocytic leukemia, unspecified
AML	C94.0	Acute erythroid leukemia
AML	C94.2	Acute megakaryoblastic leukemia
Severe Infection	A40	Streptococcal sepsis
Severe Infection	A41	Other sepsis
Severe Infection	A49	Bacterial infection of unspecified site
Severe Infection	R65	Symptoms and signs specifically associated with systemic inflammation and infection
Dialysis	CPT 1012752	Hemodialysis Procedures
Dialysis	CPT 90935	Hemodialysis procedure with single evaluation
Dialysis	CPT 90937	Hemodialysis procedure with repeated evaluation
Dialysis	SNOMED 302497006	Hemodialysis
Dialysis	SNOMED 233586004	Hemodiafiltration
Dialysis	SNOMED 233583007	Continuous hemofiltration
Dialysis	SNOMED 233585000	Continuous venovenous hemofiltration
Dialysis	SNOMED 233582002	Intermittend hemofiltration
Dialysis	ICD9 39.95	Hemodialysis
Heart failure	I50.21	Acute systolic (congestive) heart failure
Heart failure	I50.23	Acute on chronic systolic (congestive) heart failure
Heart failure	I50.31	Acute diastolic (congestive) heart failure
Heart failure	I50.33	Acute on chronic diastolic (congestive) heart failure
Heart failure	I50.41	Acute combined systolic (congestive) and diastolic (congestive) heart failure
Heart failure	I50.43	Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
Heart failure	I50.811	Acute right heart failure
Liver failure	K72.0	Acute and subacute hepatic failure without coma
Liver failure	K72	Hepatic failure, not elsewhere classified
Liver failure	K91.82	Acute and subacute hepatic failure with coma
Renal failure	N17	Acute kidney failure
Renal failure	N19	Unspecified kidney failure
Bleeding	R58	Hemorrhage, not elsewhere classified
Bleeding	K92.2	Gastrointestinal hemorrhage, unspecified
Bleeding	K13.7	Other and unspecified lesions of oral mucosa
Bleeding	J39.2	Other diseases of pharynx
Bleeding	K22.11	Ulcer of esophagus with bleeding

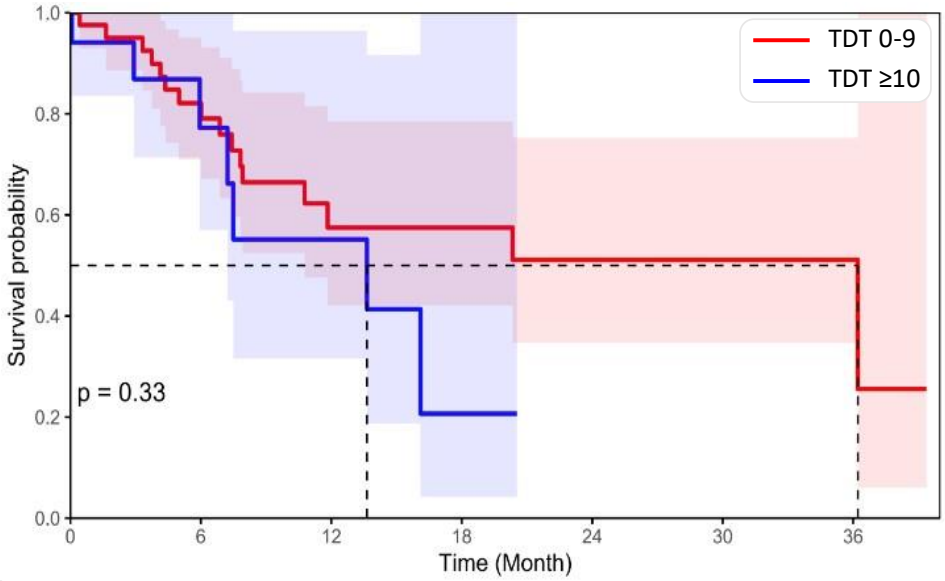
Bleeding	K29.61	Other gastritis with bleeding
Bleeding	R31	Hematuria
Bleeding	R04.0	Epistaxis
Bleeding	I61	Nontraumatic intracerebral hemorrhage
Bleeding	I60	Nontraumatic subarachnoid hemorrhage
Bleeding	K25.0	Acute gastric ulcer with hemorrhage
Bleeding	K25.2	Acute gastric ulcer with both hemorrhage and perforation
Bleeding	I62	Other and unspecified nontraumatic intracranial hemorrhage
Bleeding	K27.0	Acute peptic ulcer, site unspecific, with hemorrhage
Bleeding	K27.2	Acute peptic ulcer, site unspecific with both hemorrhage and perforation
Bleeding	K28.0	Acute gastrojejunal ulcer with hemorrhage
Bleeding	K28.2	Acute gastrojejunal ulcer with both hemorrhage and perforation
Bleeding	R04	Hemorrhage from respiratory passages
Bleeding	K62.5	Hemorrhage of anus and rectum
Bleeding	K92.2	Gastrointestinal hemorrhage, unspecified
Bleeding	H05.23	Hemorrhage of orbit
Thrombosis	I74	Arterial embolism and thrombosis
Thrombosis	I82	Other venous embolism and thrombosis
Thrombosis	I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
Thrombosis	K55.0	Acute vascular disorders of intestine
Thrombosis	I26	Pulmonary embolism
Comorbidities	E10, E11, E13	Type 1 / Type 2/ Other diabetes mellitus
Comorbidities	I50	Heart failure
Comorbidities	J44	Other chronic obstructive pulmonary disease
Comorbidities	J84	Other intestinal pulmonary disease
Comorbidities	K70	Alcoholic liver disease
Comorbidities	K71	Toxic liver disease
Comorbidities	K73	Chronic hepatitis, not elsewhere classified
Comorbidities	K74	Fibrosis and cirrhosis of liver
Comorbidities	K76.0	Fatty liver, not elsewhere classified
Comorbidities	K76.1	Chronic passive congestion of liver
Comorbidities	N18	Chronic kidney disease (CKD)
SAL Comorbidities	N18, N19	Renal Impairment
SAL Comorbidities	E08, E13	Diabetes Mellitus
SAL Comorbidities	I48, I50	Cardiac Comorbidities
SAL Comorbidities	E66	Obesity

Supplement Figure 2: Histogram start of treatment per day per group and cohort



Supplement Figure 2: Relative frequency distribution of patients receiving treatment within the first 9 days and from day 10 to day 50 per cohort and TDT group. In the SAL-cohort, median TDT was 4 days (IQR 2-6 days) in the TDT 0-9 group and 15 days (IQR 12-21 days) in the TDT ≥10 group. In the TriNetX cohort, median TDT was 3 days (IQR 1-5 days) in the TDT 0-9 group and 17 days (IQR 13-25) in the TDT ≥10 group.
* marks the median of each group. *Abbreviations: TDT:* time from diagnosis to treatment

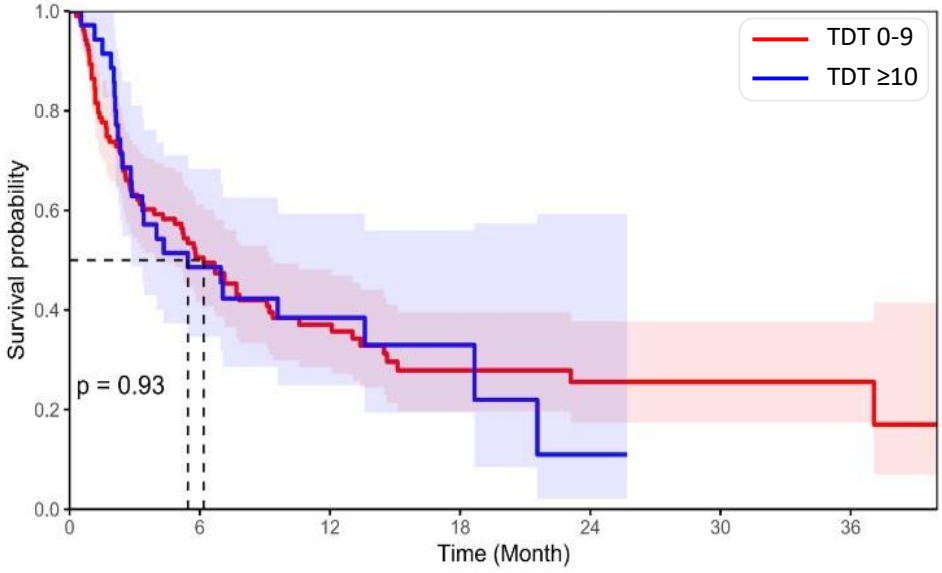
Supplement Figure 3a: Relapse-free Survival in SAL-cohort



Patients at risk

Time (Months)	0	12	24	36
TDT 0-9	44	12	6	3
TDT ≥10	17	4	0	0

Supplement Figure 3b: Event-free Survival in SAL-cohort

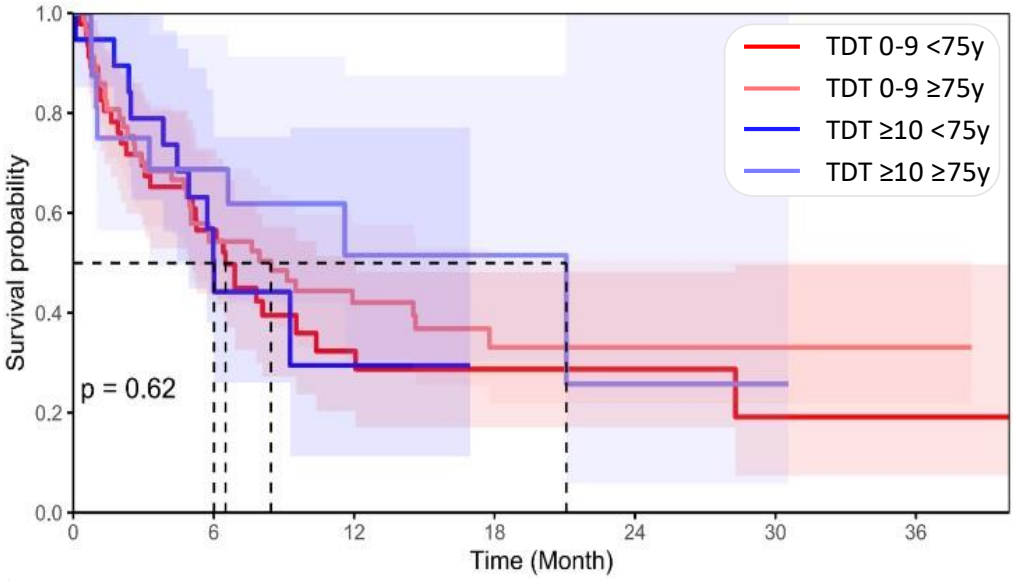


Patients at risk

Time (Months)	0	12	24	36
TDT 0-9	103	27	9	3
TDT ≥10	35	7	1	0

Supplement Figure 3: a) Relapse free survival (RFS) and b) even-free survival (EFS) of patients in the SAL-cohort. An event was defined as death, failure of primary treatment or relapse, whichever occurred first. RFS was defined as relapse after complete remission. Median RFS was 36 (95% CI 11, -) and 14 (95% CI 7.2, -) months, respectively (p=.33). RFS at 12 months was 57% (95% CI 42%, 78%) and 55% (95% CI 32%, 96%). Median EFS was 6.2 (95% CI 4.3, 9.4) months in the TDT 0-9 group and 5.5 (95% CI 2.9, -) months in the TDT ≥10 group (p=.93). EFS at 12 months was 37% (95% CI 29%, 48%) and 38% (95% CI 25%, 59%). *Abbreviations: TDT:* time from diagnosis to treatment

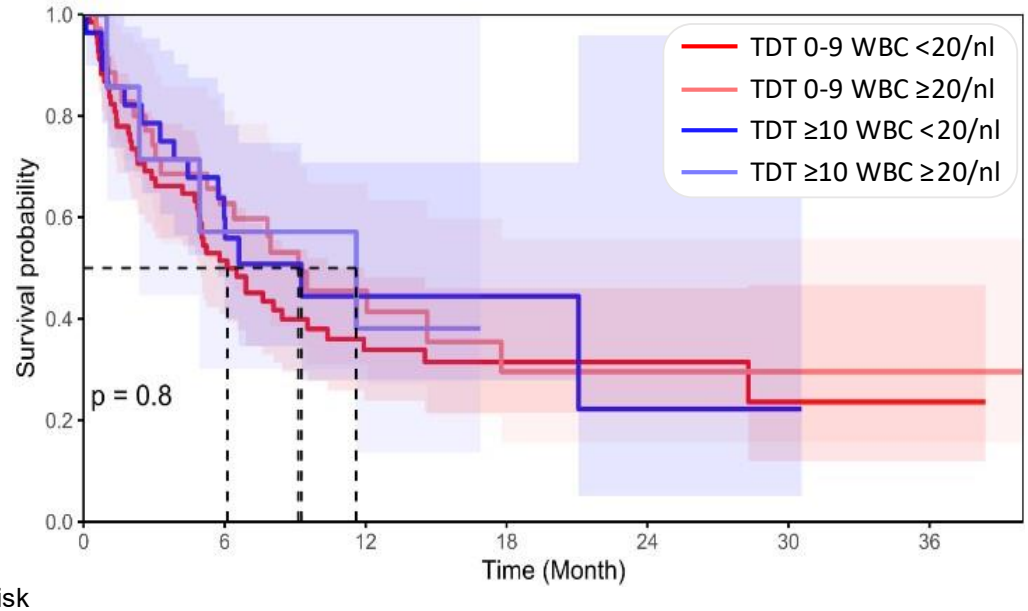
Supplement Figure 4a: Overall Survival in SAL cohort – subgroup age ≥75 years



Patients at risk

Time (Months)	0	12	24	36
TDT 0-9 <75y	46	9	3	1
TDT 0-9 ≥75y	57	18	6	1
TDT ≥10 <75y	19	2	0	0
TDT ≥10 ≥75y	16	5	1	0

Supplement Figure 4b: Overall Survival in SAL cohort – subgroup WBC ≥20x10^9/L



Patients at risk

Time (Months)	0	12	24	36
TDT 0-9 WBC<20/nl	68	16	6	1
TDT 0-9 WBC≥20/nl	35	11	3	1
TDT ≥10 WBC<20/nl	28	5	1	0
TDT ≥10 WBC≥20/nl	7	2	0	0

Supplement Figure 4: OS of a) patients aged ≥75 years and with b) WBC ≥20x10^9/L in SAL cohort. Log-rank tests between TDT 0-9 <>75 years and TDT 10-50 <>75 were not significant. Log-rank tests between TDT 0-9 <>20x10^9/L and TDT 10-50 9 <>20x10^9/L were not significant. *Abbreviations: TDT:* time from diagnosis to treatment

Supplement Table 2a: Patient characteristics subgroup age ≥75 years TriNetX

	TDT 0-9 days	TDT 10-50 days	All	p-value°
Total number, n (%)	198	106	304	
Patient characteristics				
Age (Mean ± SD)	79.1 ± 3.5	79.5 ± 3.5	79.2 ± 3.4	.29
Male, n (%)	105 (53)	57 (54)	161 (53)	.90
Female, n (%)	92 (46)	48 (45)	138 (47)	.84
BMI (Mean ± SD)	28.4 ± 5.7	28.1 ± 7.3	28.4 ± 6.1	.78
Lab. parameters (Median, IQR)				
WBC (x10^9/L)	5.2 (1.8-30.2)	3.5 (1.8-6.6)	4.1 (1.8-24.1)	
Hemoglobin (g/dl)	8.3 (7.6-9.5)	8.5 (7.7-9.7)	8.4 (7.6-9.6)	
Platelets (x10^{12}/L)	53 (31-108)	57 (24-127)	54 (26-113)	
LDH (U/L)	314 (222-548)	245 (195-428)	291 (203-496)	
Bilirubin (mg/dl)	0.6 (0.4-0.9)	0.6 (0.5-0.9)	0.6 (0.4-0.9)	
Kreatinin (mg/dl)	1.0 (0.8-1.4)	1.0 (0.8-1.2)	1.0 (0.8-1.4)	
Albumin (g/dl)	3.5 (3.1-3.9)	3.5 (3.1-3.9)	3.5 (3.1-3.9)	
CRP (mg/L) *	29 (8-100)	19 (5-129)	28 (6-100)	

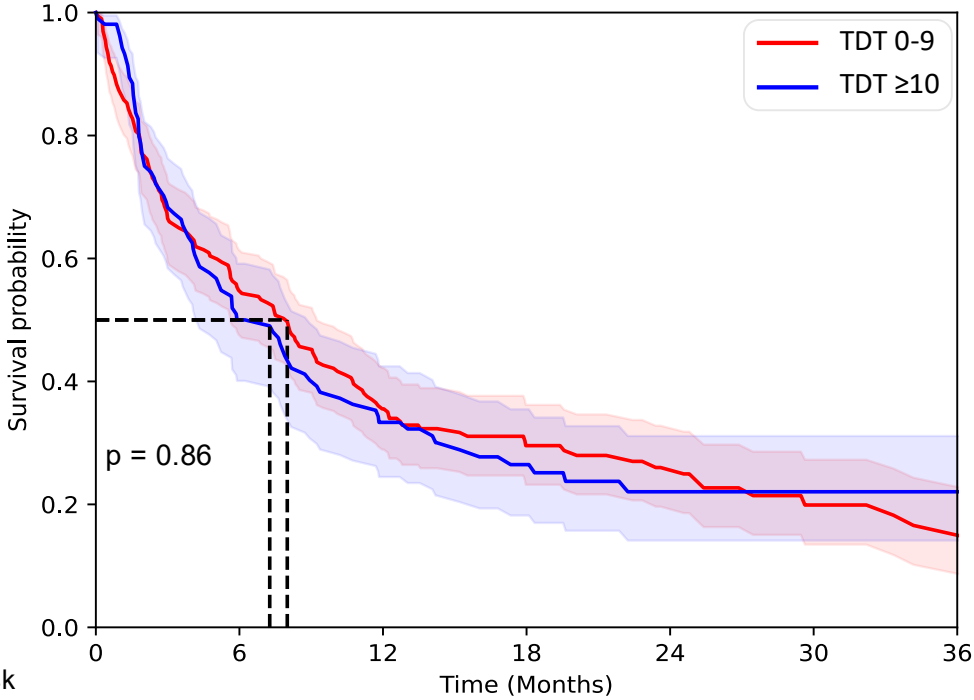
° Bonferroni-correction was used to adjust for multiple testing; p <.00625 for significance, * value available for less than 30% of patients at first diagnosis. *Abbreviations: TDT:* time from diagnosis to treatment, *WBC:* white blood cell count, *BMI:* body mass index, *LDH:* Lactate dehydrogenase, *CRP:* C-reactive protein

Supplement Table 2b: Clinical outcomes subgroup age ≥75 years TriNetX

Event (n, Risk %)	TDT 0-9 days	TDT 10-50 days	Odds ratio	95% CI
Severe Infection	63, 36.0	37, 39.8	0.85	0.51-1.43
Renal failure	46, 36.2	35, 43.8	0.81	0.46-1.43
Dialysis*	*10, 5.1	0	-	-
Liver Failure*	*10, 5.1	*10, 9.4	-	-
Heart Failure	19, 10.6	14 14.3	0.71	0.34-1.49
Bleeding	34, 22.5	20, 23.5	0.94	0.50-1.77
Thrombosis	32, 19.0	13, 15.7	1.27	0.63-2.57
HSCT*	*10, 5.1	0	-	-

* censored, number of patients 1-10. *Abbreviations: TDT:* time from diagnosis to treatment, *HSCT:* allogeneic hematopoietic stem cell transplant

Supplement Figure 5: Overall Survival in TriNetX cohort – subgroup age ≥75 years



Patients at risk

Time (Months)	0	6	12	18	24	30	36
TDT 0-9	198	109	71	40	27	14	10
TDT ≥10	106	53	35	22	14	14	14

Supplement Figure 5: Overall survival of patients aged ≥75 years in the TriNetX-cohort. Overall survival was calculated from diagnosis of AML. Median OS was 7.9 (95% CI 5.5, 9.1) months in the TDT 0-9 group and 7.2 (95% CI 4.1, 8.6) months in the TDT ≥10 group (p=.86). *Abbreviations: TDT:* time from diagnosis to treatment

Supplement Table 3a: Patient characteristics subgroup WBC ≥20x10^9/L TriNetX

	TDT 0-9 days	TDT 10-50 days	All	p-value°
Total number, n (%)	162	35	217	
Patient characteristics				
Age (Mean ±SD)	72.8 ± 7.2	70.2 ± 11.8	72.4 ± 8.2	.088
Male, n (%)	89 (55)	21 (60)	110 (56)	.58
Female, n (%)	73 (45)	14 (40)	87 (46)	.58
BMI (Mean ±SD)	28.6 ± 6.6	27.7 ± 8.0	28.7 ± 6.6	.68
Lab. parameters (Median, IQR)				
WBC (x10^9/L)	40 (24-63)	61 (26-103)	43 (24-63)	
Hemoglobin (g/dl)	8.0 (7.4-9.2)	8.4 (7.4-8.9)	8.0 (7.3-9.1)	
Platelets (x10^{12}/L)	42 (26-70)	37 (16-65)	40 (23-67)	
LDH (U/L)	598 (376-1070)	986 (590-1706)	625 (394-1109)	
Bilirubin (mg/dl)	0.7 (0.4-0.9)	0.6 (0.4-0.9)	0.6 (0.4-0.9)	
Kreatinin (mg/dl)	1.1 (0.86-1.68)	0.97 (0.78-1.26)	1.02 (0.80-1.66)	
Albumin (g/dl)	3.3 (2.8-3.6)	3.2 (2.9-3.5)	3.2 (2.9-3.6)	
CRP (mg/L) *	47 (20-100)	83 (0-118)	83 (20-118)	

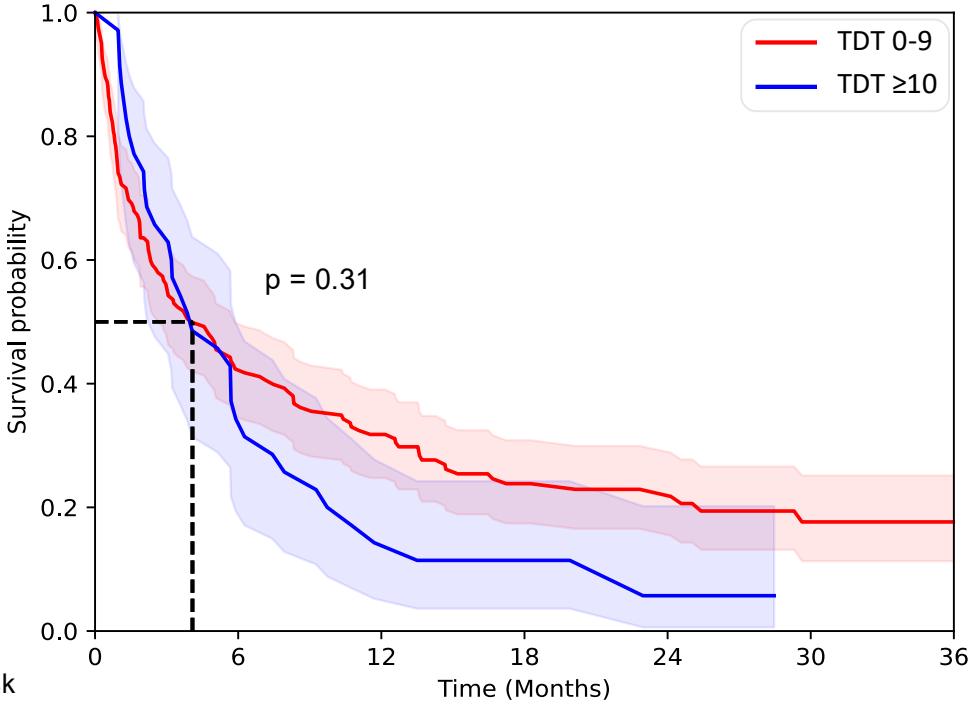
° Bonferroni-correction was used to adjust for multiple testing; p <.00625 for significance, * value available for less than 30% of patients at first diagnosis. *Abbreviations: TDT:* time from diagnosis to treatment *WBC:* white blood cell count, *BMI:* body mass index, *LDH:* Lactate dehydrogenase, *CRP:* C-reactive protein

Supplement Table 3b: Clinical outcomes subgroup WBC ≥20x10^9/L TriNetX

Event (n, Risk %)	TDT 0-9 days	TDT 10-50 days	Odds ratio	95% CI
Severe Infection	53, 38.4	16, 57.1	0.47	0.21-1.07
Renal failure	26, 28.9	*10, 41.7	-	-
Dialysis*	*10, 6.2	*10, 28.6	-	-
Liver Failure*	*10, 6.3	*10, 28.6	-	-
Heart Failure*	12, 8.28	*10, 29.4	-	-
Bleeding*	33, 26.2	*10, 43.5	-	-
Thrombosis*	29, 21.8	*10, 40.0	-	-
HSCT*	*10, 6.2	*10, 28.6	-	-

* censored, number of patients 1-10. *Abbreviations: TDT:* time from diagnosis to treatment, *HSCT:* allogeneic hematopoietic stem cell transplant

Supplement Figure 6: Overall Survival in SAL cohort – subgroup WBC ≥20x10^9/L



Patients at risk

Time (Months)	0	6	12	18	24	30	36
TDT 0-9	162	69	52	31	26	11	11
TDT ≥10	35	13	6	5	2	-	-

Supplement Figure 6: Overall survival of patients with WBC ≥20x10^9/L in the TriNetX-cohort. Overall survival was calculated from diagnosis of AML. Median OS was 4.0 (95% CI 2.5, 5.7) months in the TDT 0-9 group and 4.0 (95% CI 2.1, 5.6) months in the TDT ≥10 group (p=.31). *Abbreviations: TDT:* time from diagnosis to treatment

Supplement Table 4a: Patient characteristics subgroup comorbidities TriNetX

	TDT 0-9 days	TDT 10-50 days	All	p-value°
Total number, n (%)	323	152	475	
Patient characteristics				
Age (Mean ±SD)	71.5 ± 8.33	72.7 ± 9.61	71.9 ± 8.77	.14
Male, n (%)	187 (57)	98 (64)	285 (60)	.24
Female, n (%)	136 (43)	54 (36)	190 (40)	.24
BMI (Mean ±SD)	30.2 ± 7.0	27.1 ± 6.5	30.0 ± 7.1	.01
Lab. parameters (Median, IQR)				
WBC (x10^9/L)	5.4 (2.1-28.4)	3.4 (1.4-7.4)	4.1 (1.6-24.0)	
Hemoglobin (g/dl)	8.1 (7.6-9.4)	8.5 (7.8-9.3)	8.3 (7.6-9.4)	
Platelets (x10^{12}/L)	43 (24-92)	51 (21-98)	46 (24-96)	
LDH (U/L)	352 (226-474)	251 (178-463)	320 (209-602)	
Bilirubin (mg/dl)	0.6 (0.5-0.9)	0.6 (0.4-0.9)	0.6 (0.4-0.9)	
Kreatinin (mg/dl)	1.0 (0.76-1.4)	0.93 (0.74-1.3)	1.0 (0.76-1.4)	
Albumin (g/dl)	3.4 (3.0-3.9)	3.6 (3.2-4.0)	3.5 (3.1-3.9)	
CRP (mg/L) *	47 (20-125)	38 (5-83)	28 (9-118)	

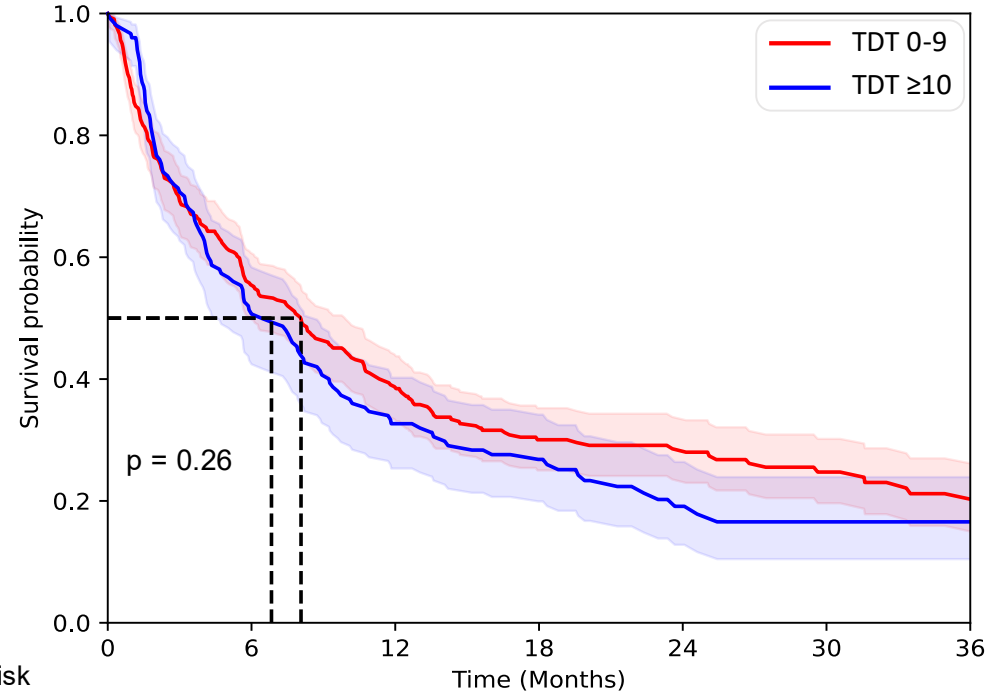
° Bonferroni-correction was used to adjust for multiple testing; p <.00625 for significance, * value available for less than 30% of patients at first diagnosis. *Abbreviations: TDT:* time from diagnosis to treatment, *WBC:* white blood cell count, *BMI:* body mass index, *LDH:* Lactate dehydrogenase, *CRP:* C-reactive protein

Supplement Table 4b: Clinical outcomes subgroup comorbidities TriNetX

Event (n, Risk %)	TDT 0-9 days	TDT 10-50 days	Odds ratio	95% CI
Severe Infection	131, 45.6	66, 49.6	0.85	0.57-1.29
Renal failure	122, 56.2	57, 49.6	1.31	0.83-2.06
Dialysis*	*10, 3.10	*10, 6.60	-	-
Liver Failure*	19, 5.92	*10, 6.60	-	-
Heart Failure	41, 14.2	28, 19.9	0.67	0.39-1.14
Bleeding	85, 34.4	28, 24.3	1.63	0.99-2.69
Thrombosis	61, 22.7	24, 20.2	1.16	0.68-1.97
HSCT*	18, 5.59	*10, 6.58	-	-

* censored, number of patients 1-10. *Abbreviations: TDT:* time from diagnosis to treatment, *HSCT:* allogeneic hematopoietic stem cell transplant

Supplement Figure 7: Overall Survival in TriNetX cohort – subgroup comorbidities



Patients at risk

Time (Months)	0	6	12	18	24	30	36
TDT 0-9	323	178	123	73	52	32	24
TDT ≥10	152	77	50	35	18	14	14

Supplement Figure 7: Overall survival of patients with comorbidities in the TriNetX-cohort. Overall survival was calculated from diagnosis of AML. Median OS was 7.9 (95% CI 5.8, 9.7) months in the TDT 0-9 group and 6.7 (95% CI 4.3, 8.1) months in the TDT ≥10 group (p=.26). *Abbreviations: TDT:* time from diagnosis to treatment