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

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Received: February 6, 2024.
Accepted: April 17, 2024.
Early view: April 24, 2024.

https://doi.org/10.3324/haematol.2024.285225

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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.

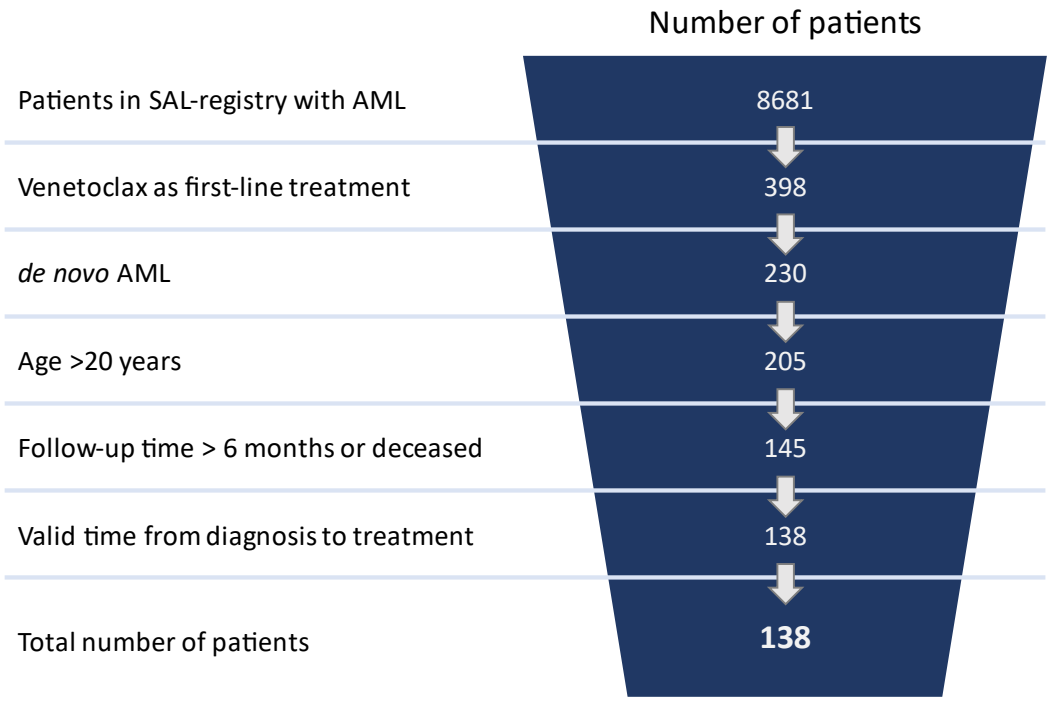
Statistical analysis TriNetX-cohort
The ICD and procedure codes used for analyses are listed in the Supplement Table 1. To improve the validity of data and account for potential documentation errors, we excluded patients from analysis who received treatment >50 days after diagnosis. Patients were assigned 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.

References:

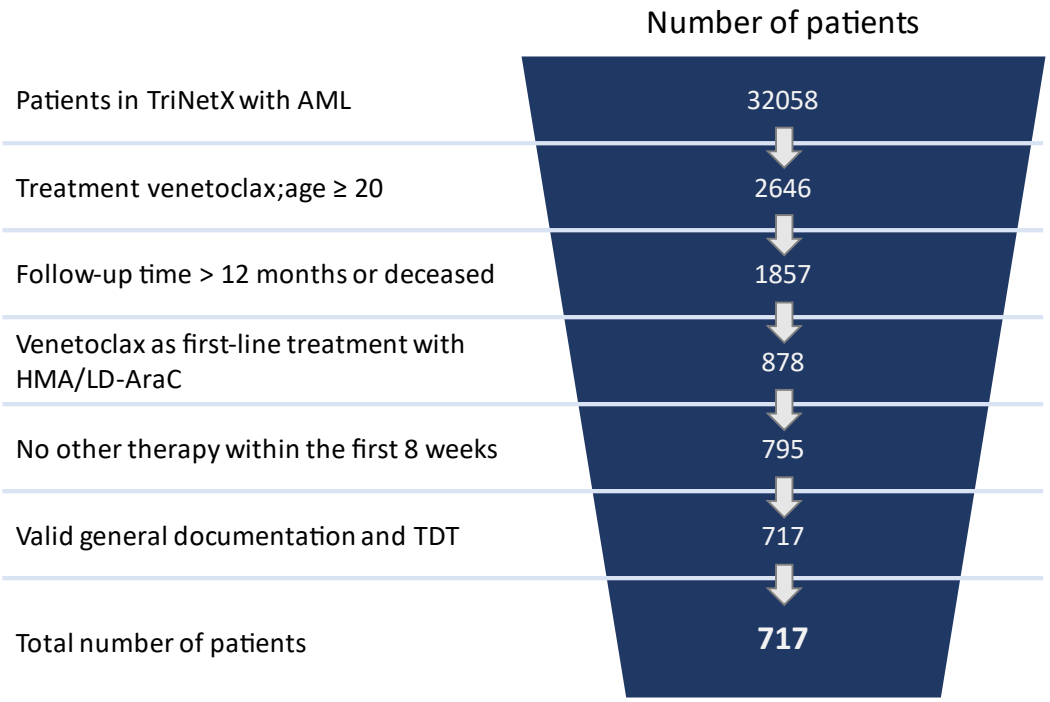
1. Voso MT, Ferrara F, Galimberti S, Rambaldi A, Venditti A. Diagnostic Workup of Acute Myeloid Leukemia: What Is Really Necessary? An Italian Survey. Front Oncol;12.

2. Dutcher JP, Schiffer CA, Wiernik PH. Hyperleukocytosis in adult acute nonlymphocytic leukemia: impact on remission rate and duration, and survival. J Clin Oncol Off J Am Soc Clin Oncol 1987;5(9):1364–1372.

Supplement Figure 1a: Patient selection SAL



Supplement Figure 1b: Patient selection TriNetX

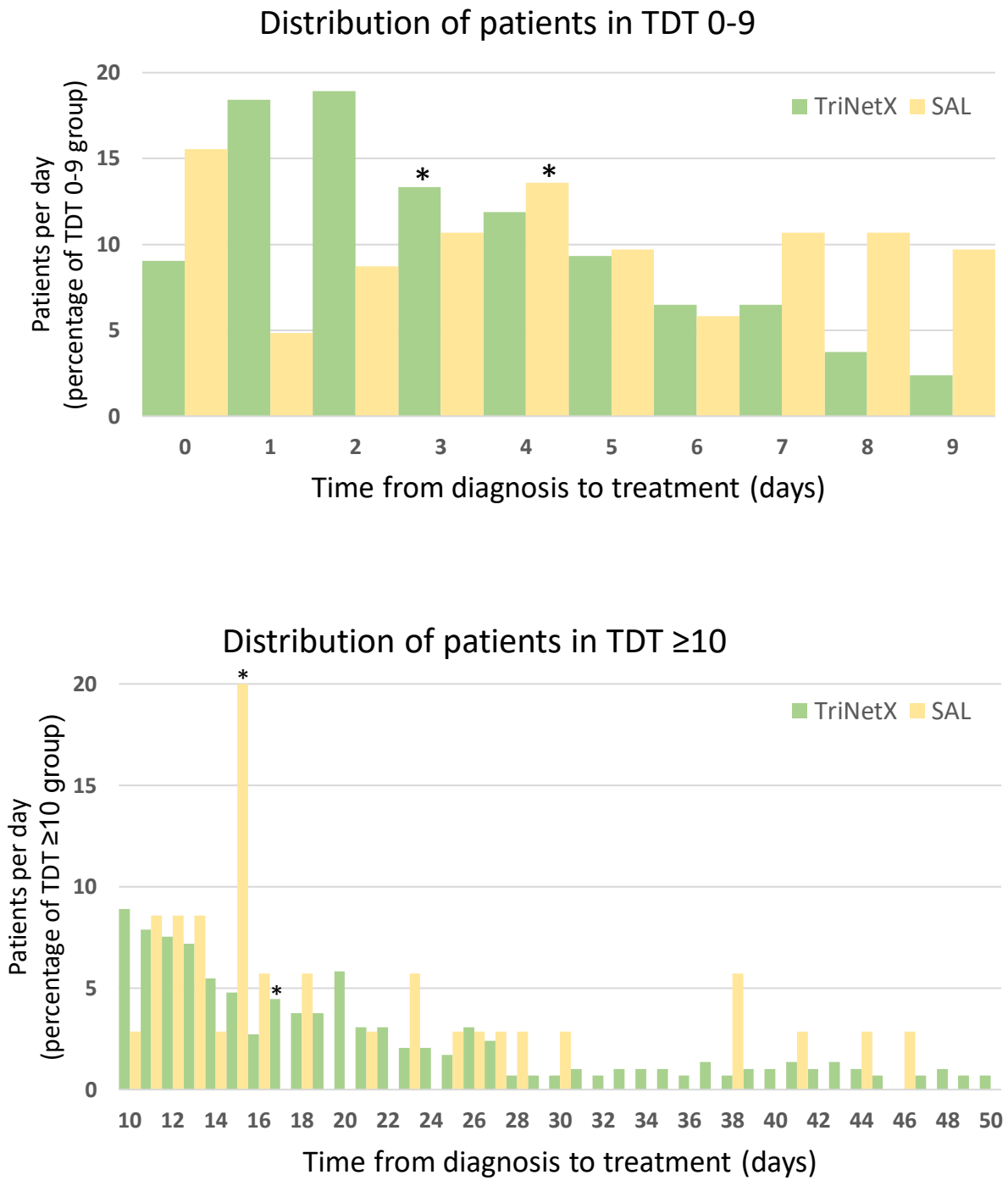


Supplement Table 1: List of ICD-10-CM and procedural codes used for TriNetX and SAL

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

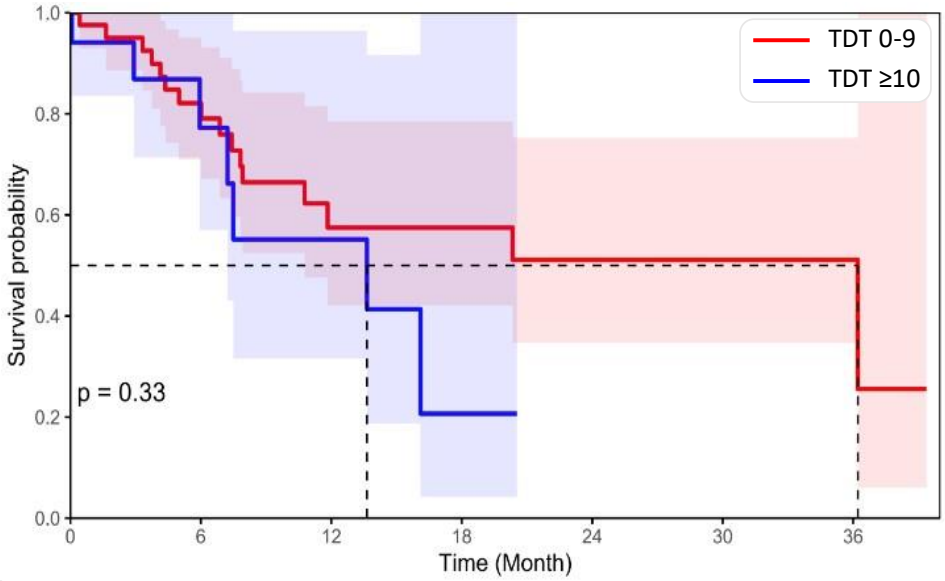
Bleeding	K29.61	Other gastritis with bleeding
Bleeding	R31	Hematuria
Bleeding	R04.0	Epistaxis
Bleeding	I61	Nontraumatic intracerebral hemorrhage
Bleeding	I60	Nontraumatic subarachnoid hemorrhage
Bleeding	K25.0	Acute gastric ulcer with hemorrhage
Bleeding	K25.2	Acute gastric ulcer with both hemorrhage 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

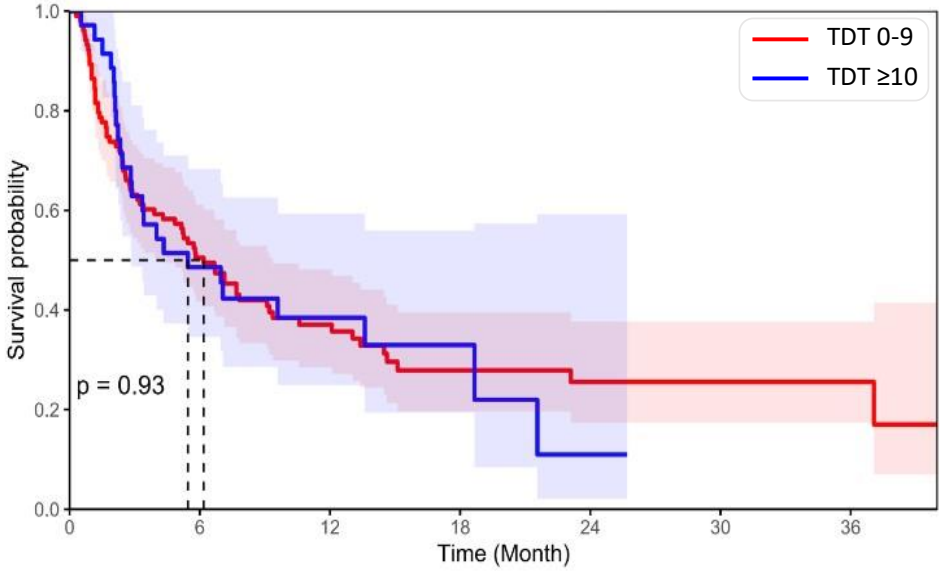
Supplement Figure 3a: Relapse-free Survival in SAL-cohort



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

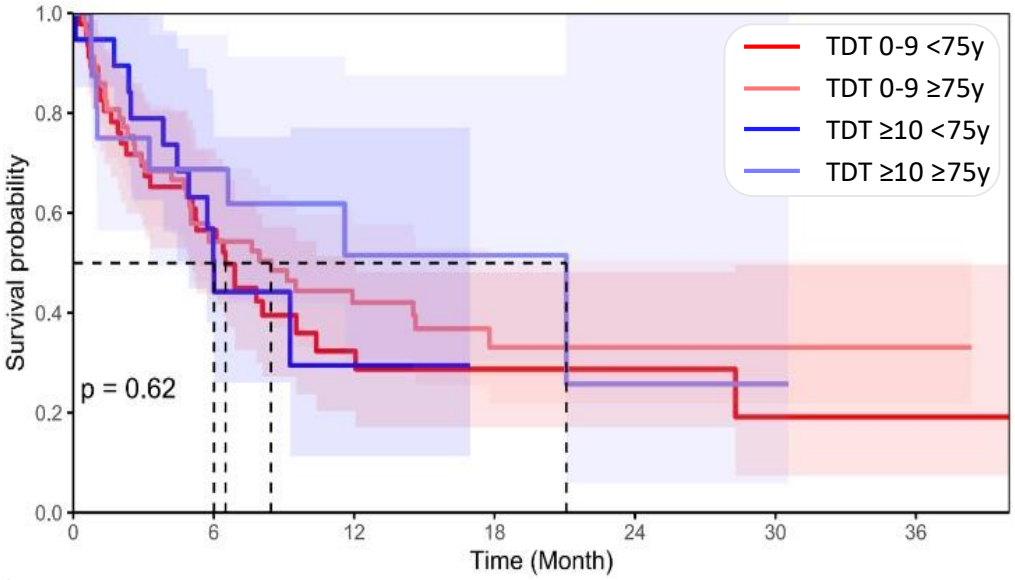


Patients at risk

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

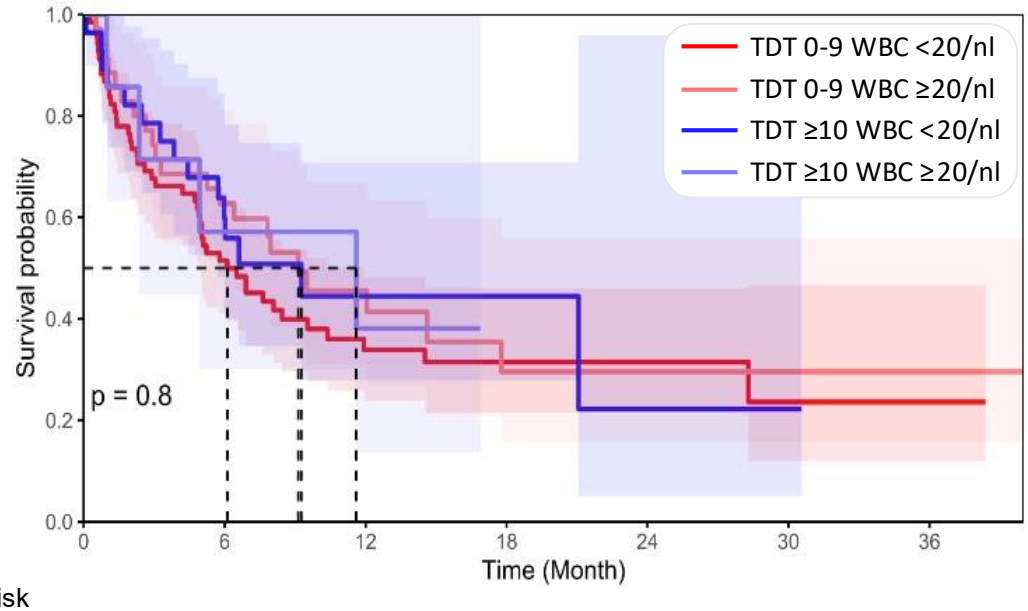
Supplement Figure 4a: Overall Survival in SAL cohort – subgroup age ≥75 years



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)	

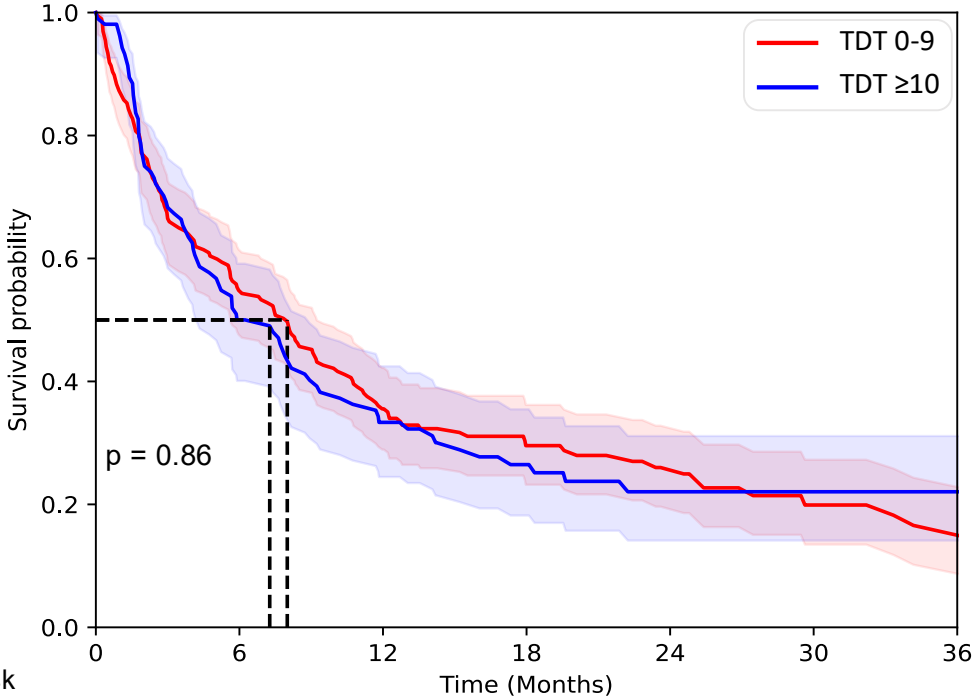
° Bonferroni-correction was used to adjust for multiple testing; p <.00625 for significance, * value available for less than 30% of patients at first diagnosis. *Abbreviations: TDT:* time from diagnosis to treatment, *WBC:* white blood cell count, *BMI:* body mass index, *LDH:* Lactate dehydrogenase,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

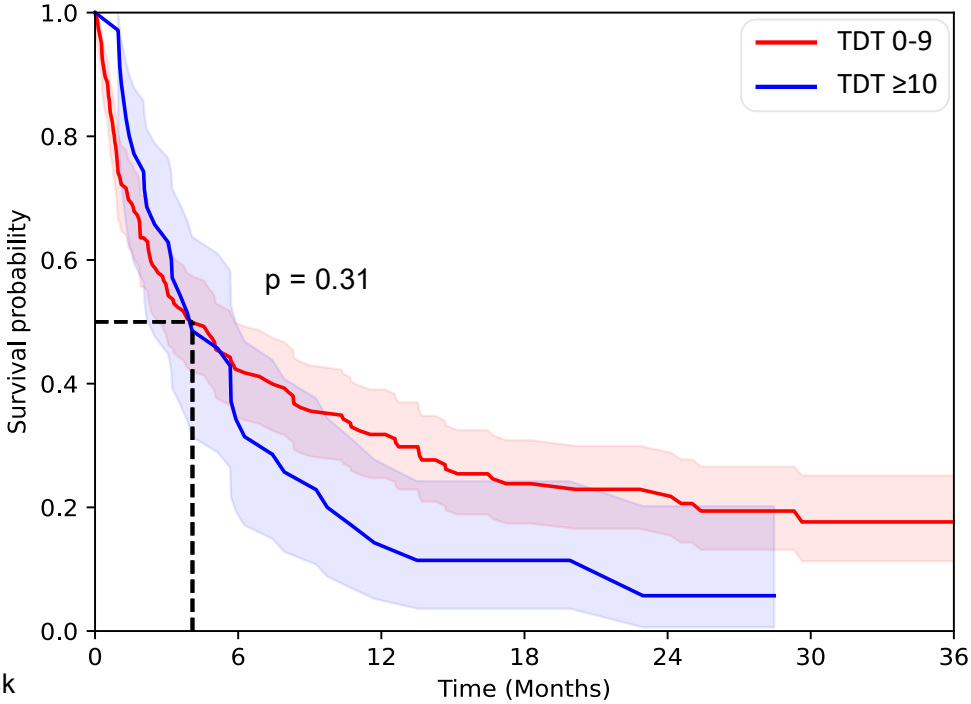
° Bonferroni-correction was used to adjust for multiple testing; p <.00625 for significance, * value available for less than 30% of patients at first diagnosis. *Abbreviations: TDT:* time from diagnosis to treatment *WBC:* white blood cell count, *BMI:* body mass index, *LDH:* Lactate dehydrogenase,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

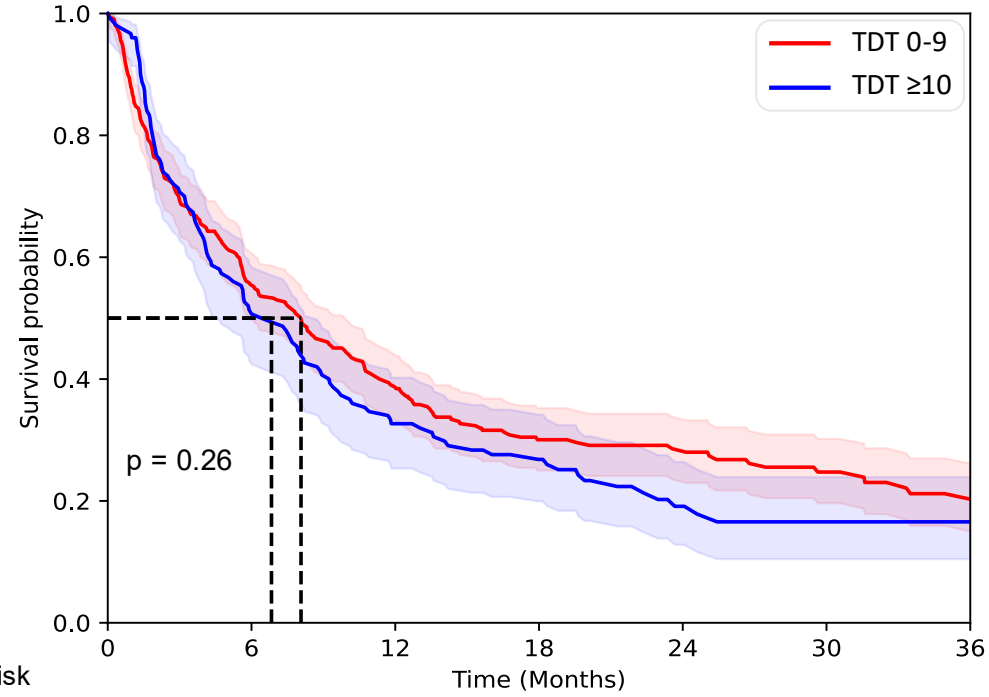
° Bonferroni-correction was used to adjust for multiple testing; p <.00625 for significance, * value available for less than 30% of patients at first diagnosis. *Abbreviations: TDT:* time from diagnosis to treatment, *WBC:* white blood cell count, *BMI:* body mass index, *LDH:* Lactate dehydrogenase,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