No impact of time from diagnosis to treatment on survival in newly diagnosed AML treated with venetoclax-based regimens - Supplement

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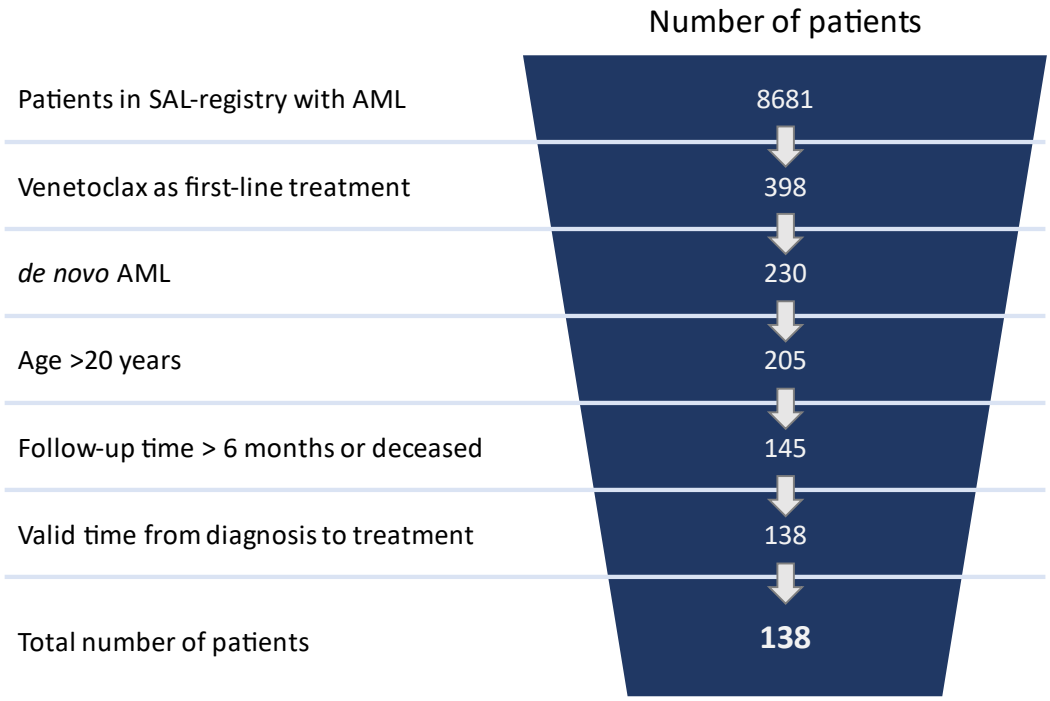
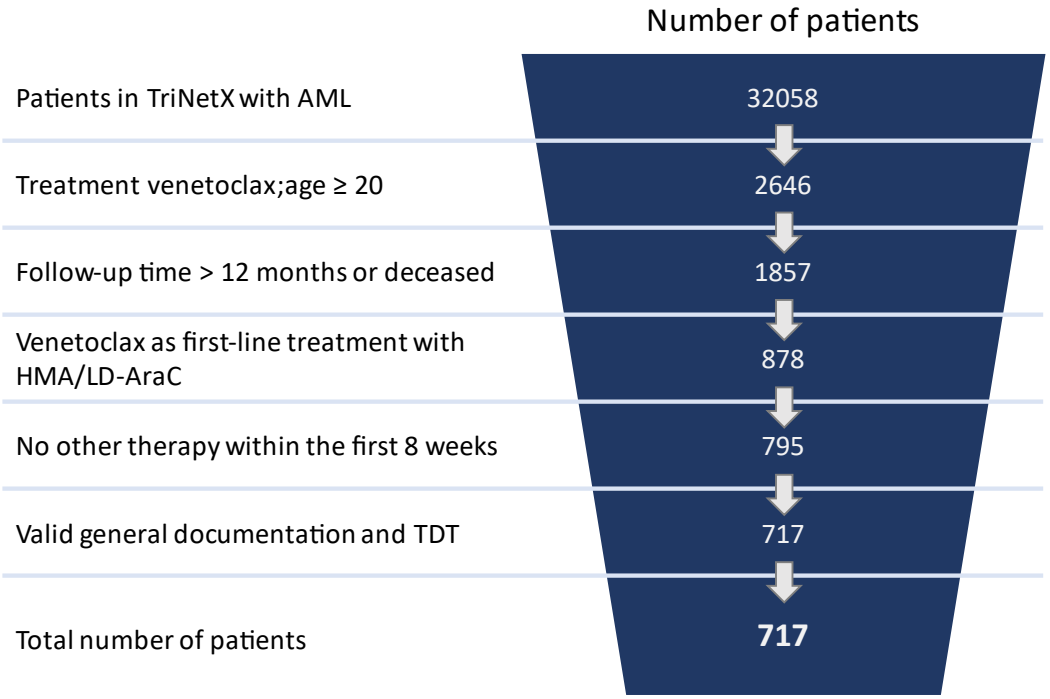
Supplement Figure 1a: Patient selection SAL



Supplement Figure 1b: Patient selection TriNetX

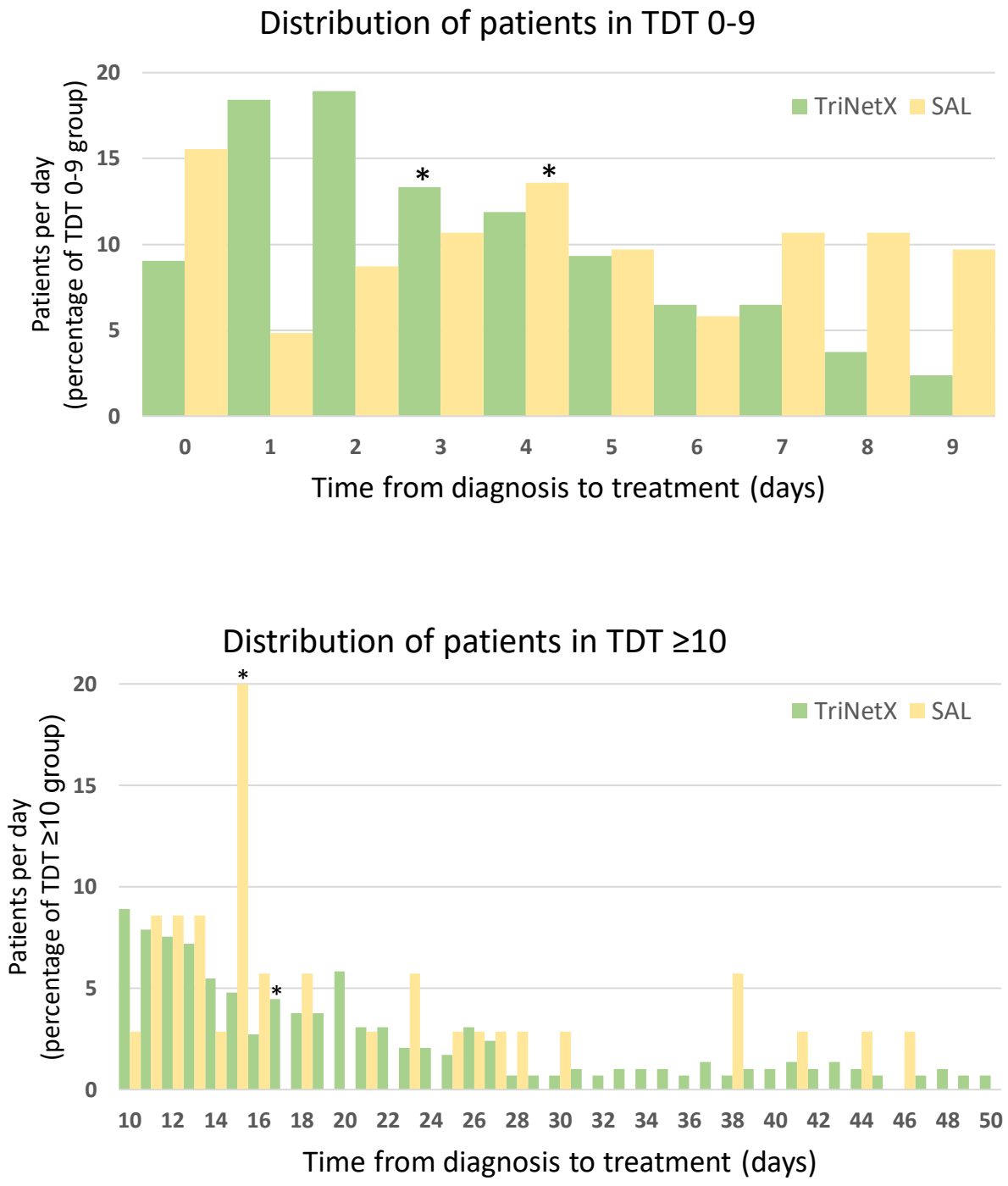


Supplement Table 1: List of ICD-10-CM and procedural codes used for TriNetX and SAL

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

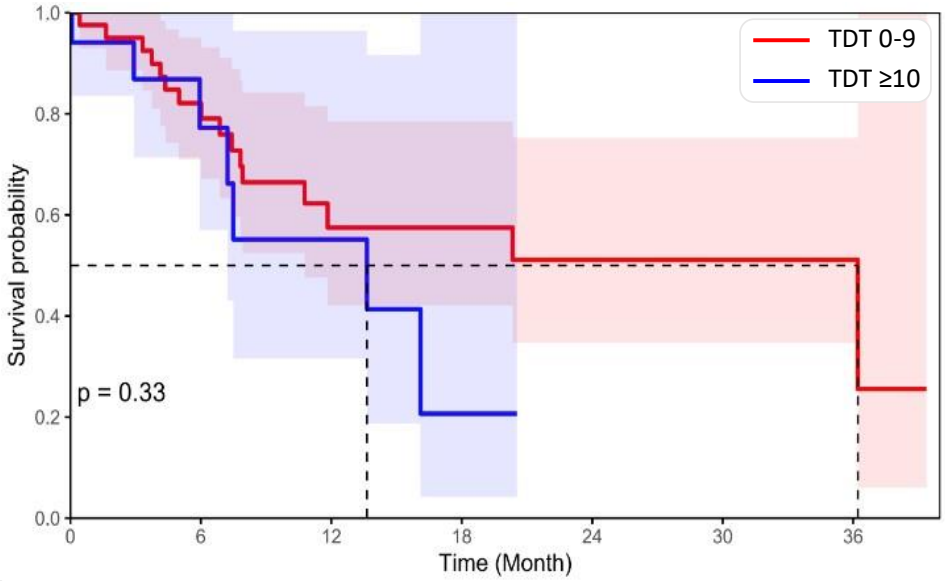
Bleeding	K29.61	Other gastritis with bleeding
Bleeding	R31	Hematuria
Bleeding	R04.0	Epistaxis
Bleeding	I61	Nontraumatic intracerebral hemorrhage
Bleeding	I60	Nontraumatic subarachnoid hemorrhage
Bleeding	K25.0	Acute gastric ulcer with hemorrhage
Bleeding	K25.2	Acute gastric ulcer with both hemorrhage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

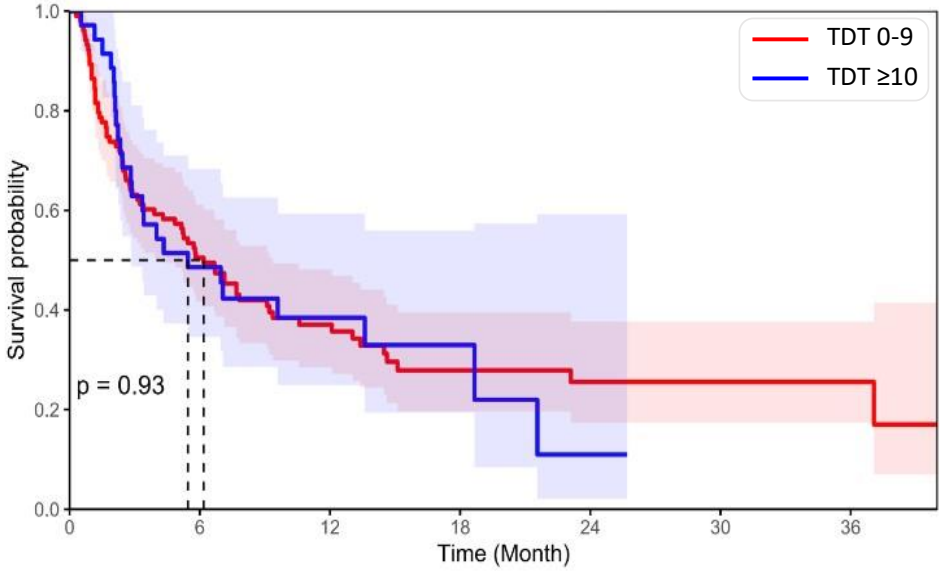
Supplement Figure 3a: Relapse-free Survival in SAL-cohort



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

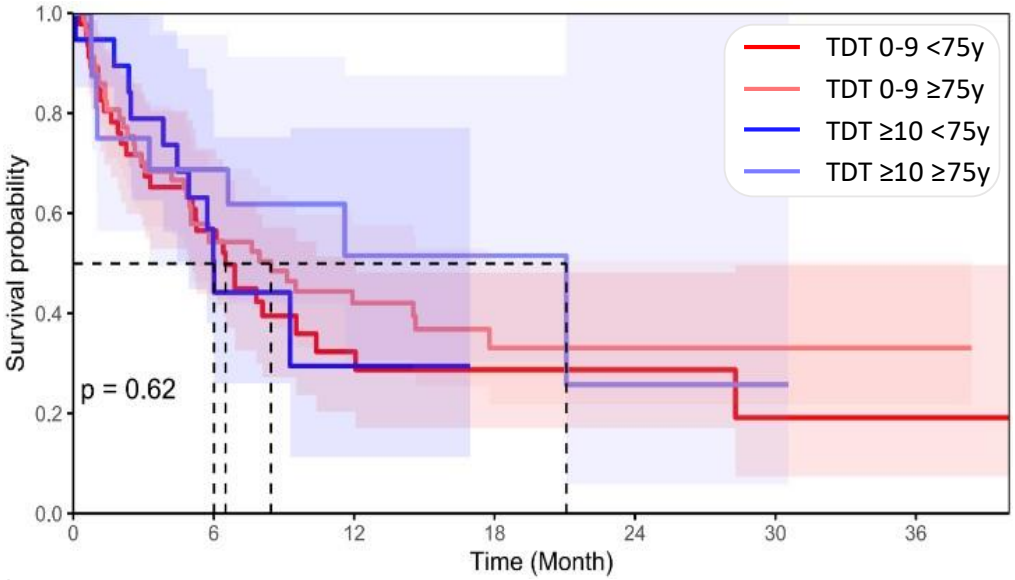


Patients at risk

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%).

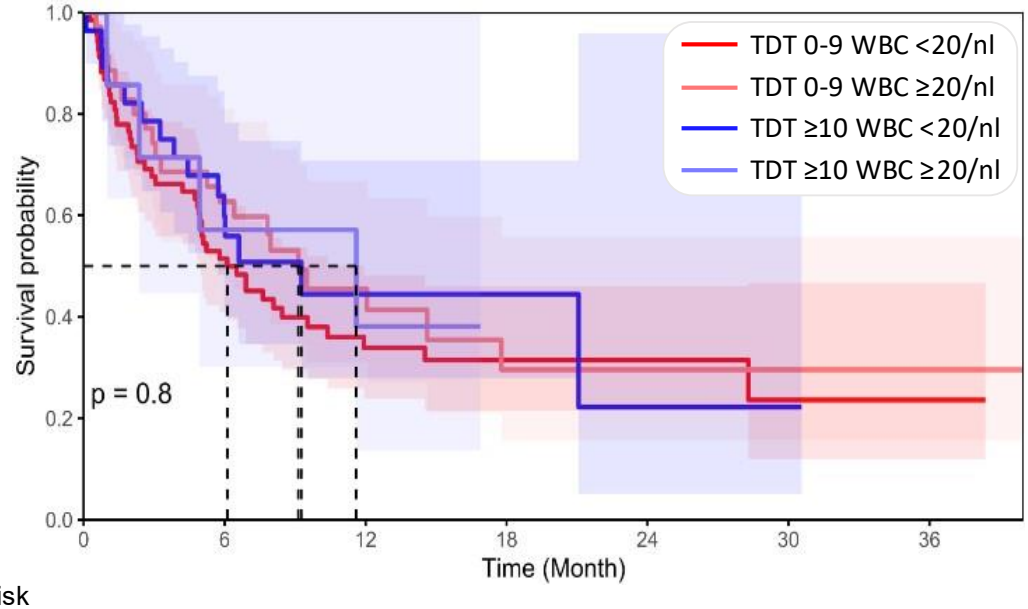
Supplement Figure 4a: Overall Survival in SAL cohort – subgroup age ≥75 years



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 ≥20/nl



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 ≥20/nl 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 <>20/nl and TDT 10-50 9 <>20/nl were not significant.

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 (/nl)	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 (x10³/nl)	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)	

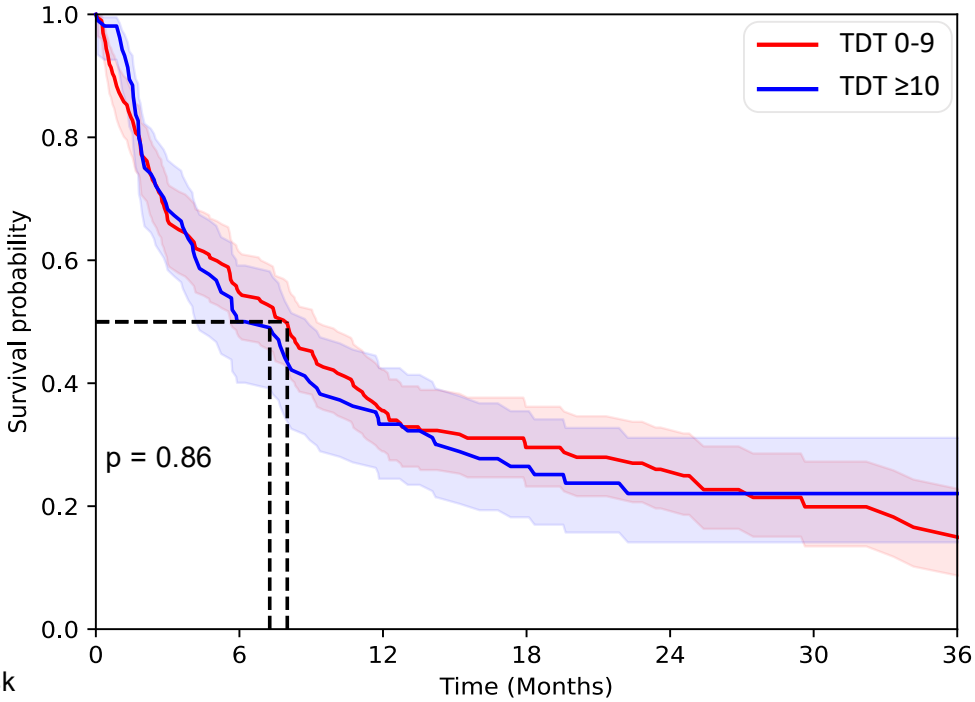
° Bonferroni-correction was used to adjust for multiple testing; p <.00625 for significance, * value available for less than 30% of patients at first diagnosis. *Abbreviations: WBC:* white blood cell count, *BMI:* body mass index, *LDH:* Lactate dehydrogenase, *CRP:* C-reactive protein

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

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).

Supplement Table 3a: Patient characteristics subgroup WBC≥20/nl 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 (/nl)	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 (x10³/nl)	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)	

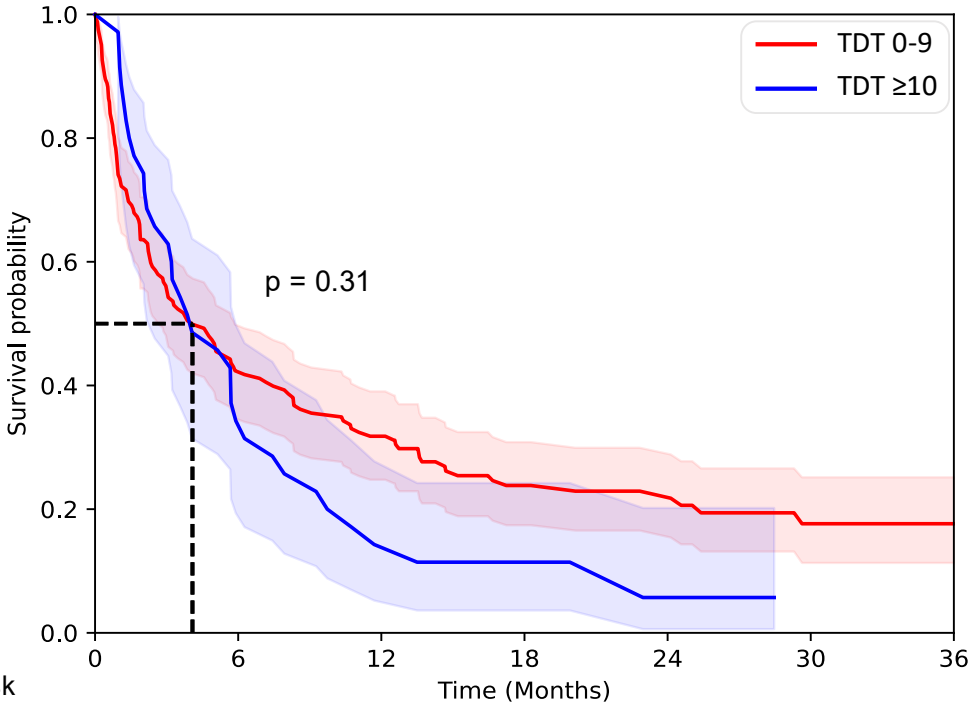
° Bonferroni-correction was used to adjust for multiple testing; p <.00625 for significance, * value available for less than 30% of patients at first diagnosis. *Abbreviations: WBC:* white blood cell count, *BMI:* body mass index, *LDH:* Lactate dehydrogenase, *CRP:* C-reactive protein

Supplement Table 3b: Clinical outcomes subgroup WBC≥20/nl 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

Supplement Figure 6: Overall Survival in SAL cohort – subgroup WBC ≥20/nl



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 ≥20/nl 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).

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 (/nl)	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 (x10³/nl)	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)	

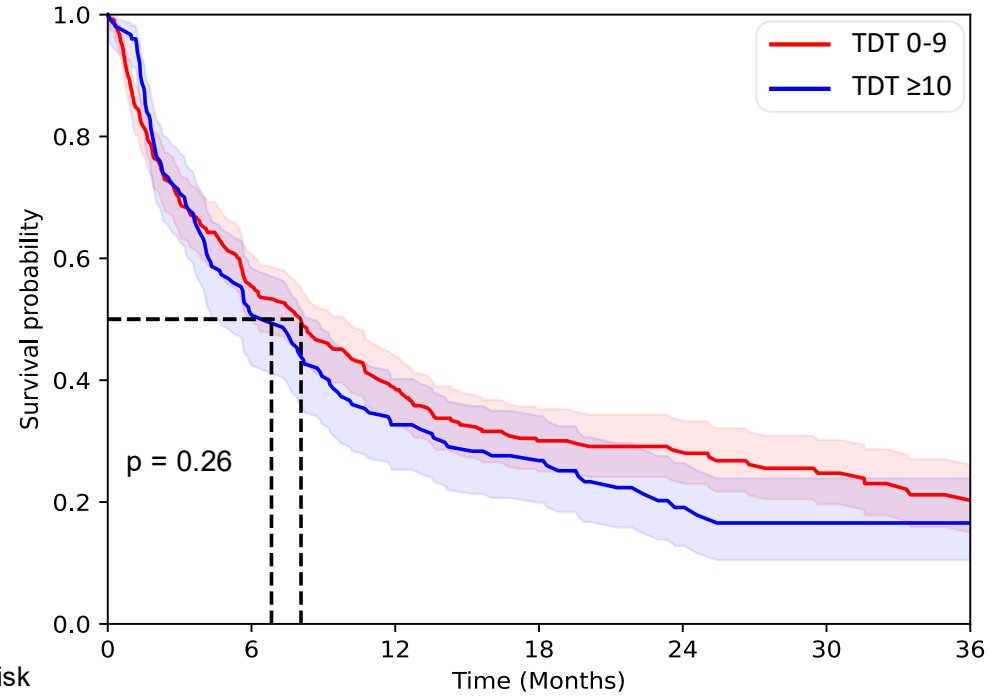
° Bonferroni-correction was used to adjust for multiple testing; p <.00625 for significance, * value available for less than 30% of patients at first diagnosis. *Abbreviations: WBC:* white blood cell count, *BMI:* body mass index, *LDH:* Lactate dehydrogenase, *CRP:* C-reactive protein

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

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).