Supporting Information for the original research article titled:

Asparaginase formulation impacts hypertriglyceridemia during therapy for acute lymphoblastic leukemia

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Supporting Methods

Asparaginase allergy and substitution

In TXV, patients with allergic reaction to *E. coli* L-asparaginase were subsequently given *Erwinia* L-asparaginase: 20,000 U/m^2/dose (IM administration) in LR cases during reinduction; and at 25,000 U/m^2 twice weekly (3 to 4 days apart) from weeks 1 to 19 of continuation treatment in SHR patients. Patients allergic to both *E. coli* and *Erwinia* preparations were given PEG-asparaginase (at 2500 U/m^2 per week by IV administration).

In TXVI, patients with allergic reaction to PEG-asparaginase were subsequently given *Erwinia* L-asparaginase. During continuation therapy, in patients that were randomized to 2,500 U/m^2, each dose of PEG was replaced by *Erwinia* at 30,000 U/m^2/dose twice weekly (3 to 4 days apart) for 4 doses. In patients randomized to 3,500 U/m^2, each dose of PEG was replaced by *Erwinia* at 42,000 U/m^2/dose twice weekly (3 to 4 days apart) for 4 doses.

Genotyping

Germline DNA from blood was genotyped using the Exome-24 BeadChip (Illumina, San Diego, CA) and either the Affymetrix Genome-Wide Human SNP Array 6.0 or the Affymetrix Human Mapping 500K Array Set (Affymetrix, Santa Clara, CA) as described previously [1]. The Michigan Imputation Server was used to impute remaining untyped SNPs [2]. The Hardy-Weinberg equilibrium (HWE) test was performed using PLINK on

SNPs with an MAF ≥ 1% and among patients of European ancestry. SNPs that were not in HWE ($P < 0.001$) were excluded from the association analysis.

Ancestry

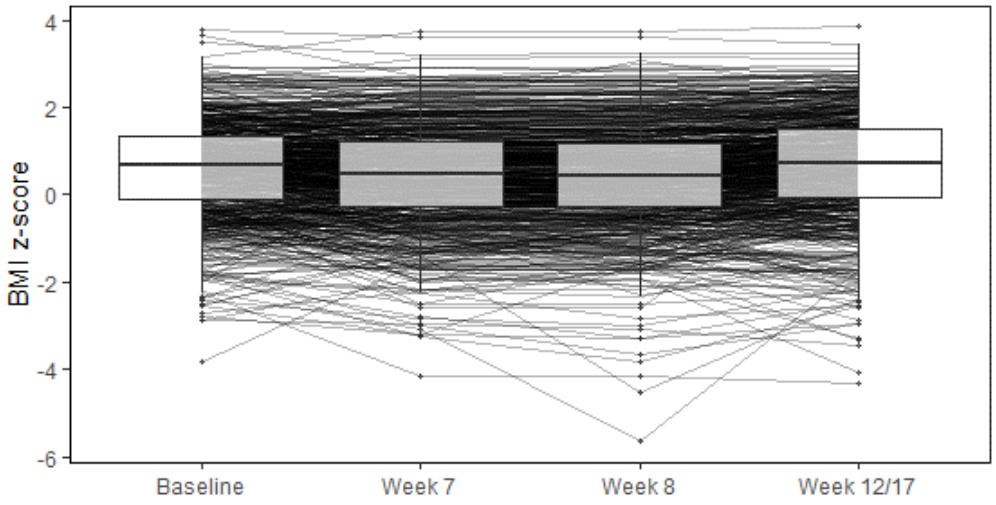
Percent ancestry was treated as a continuous variable or used to assign patients to race groups: >90% Northern European ancestry were classified as white; >70% West African ancestry were classified as black; >10% Native American ancestry and greater Native American ancestry than West African ancestry were classified as Hispanic; patients not falling into one of these groups were categorized as other [3-5].

Polygenic risk score for elevated triglycerides

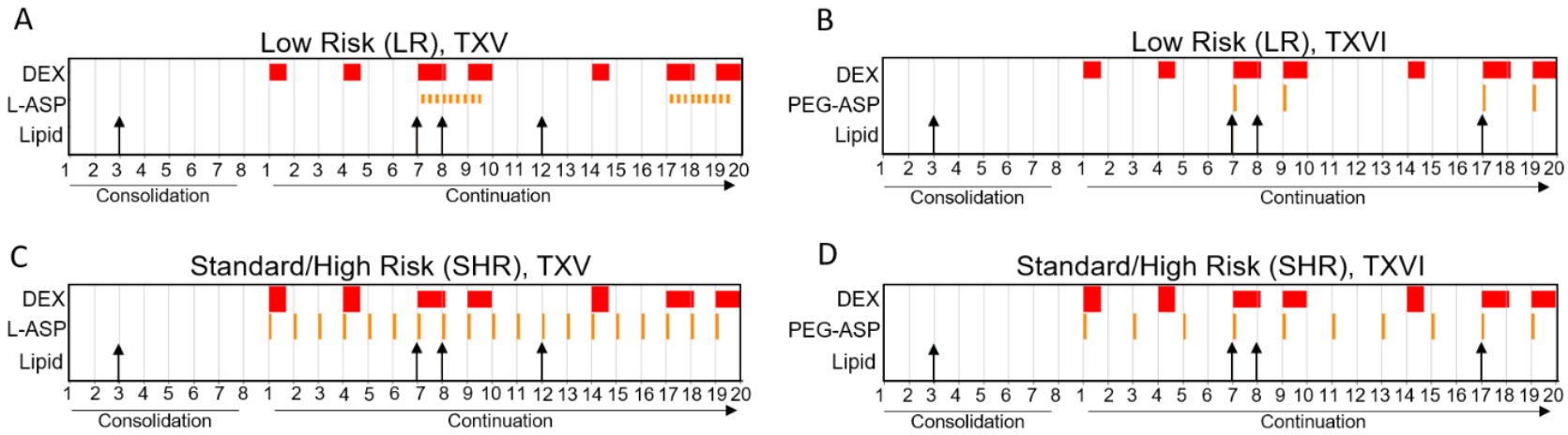
Weighted polygenic risk scores for elevated triglycerides (triglyceride-PRS) were generated from 16 SNPs reported to be associated with increased triglycerides in the general European population [6,7] (Supplemental Table 2). At a locus the number of triglyceride-raising alleles (0, 1, or 2) was multiplied by the reported beta coefficient (effect size) [7] and then summed across all 16 loci. Polygenic risk scores were only generated for white patients as the reference populations were of European ancestry [6,7].

Genome-wide statistical analyses

The genome-wide association analyses between SNP genotypes and maximum triglyceride was performed in PLINK 1.9 [8] using linear or logistic regression as appropriate, adjusting for significant covariates and assuming an additive genetic model[8]. Genome-wide significance threshold was set at a p-value of $<5x10^{-8}$.

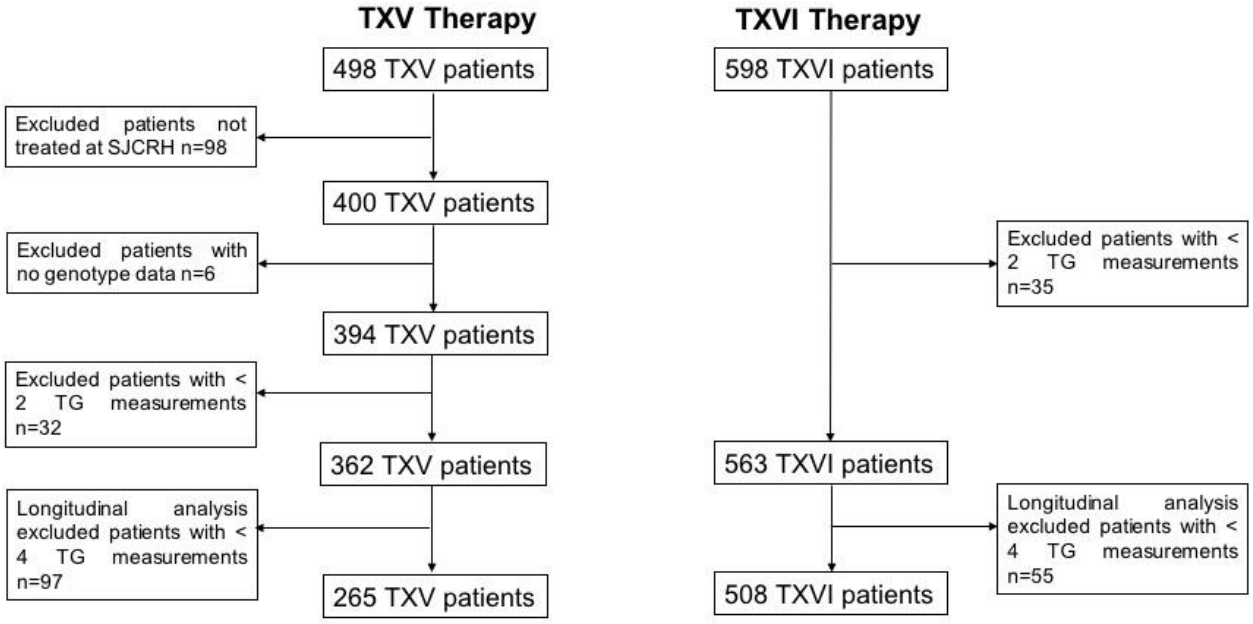


Supporting Information Figure S1: BMI (z-score) did not change over the observed course of therapy. BMI z-score, derived using the R childsds package [9], shown for patients > 2 years of age on TXV or TXVI therapy. Only patients with BMI information at all four time points were included. N= 771.

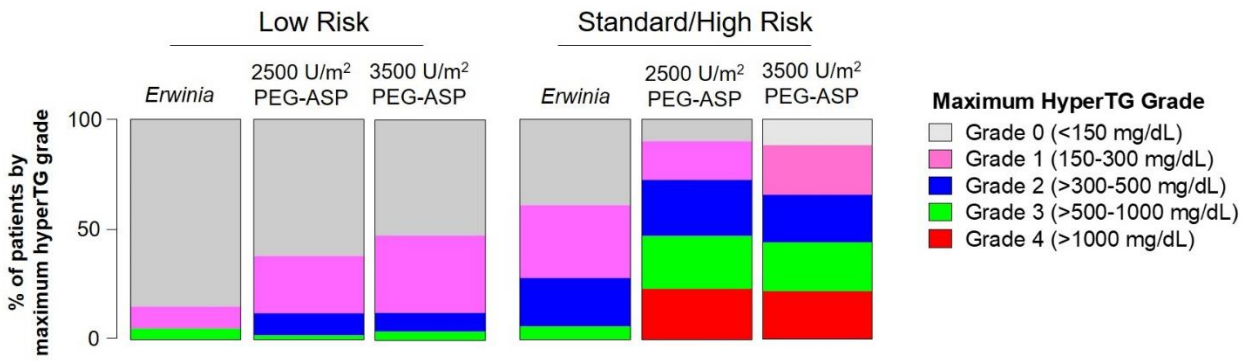


Supporting Information Figure S2: Drug regimens and triglyceride measurements by protocol and risk-arm. Triglycerides (TG) were measured in all patients at: consolidation day 15 ("baseline" was > 35 days after the last dose of asparaginase (ASP) and > 21 days after the last dose of glucocorticoid); day 1 of week 7 (TXV LR, 15 weeks after the last asparaginase dose and 2 weeks from the start of the last dexamethasone course; TXV SHR, 1 week after the last asparaginase dose and 2 weeks from the start of the last dexamethasone course; TXVI LR, 15 weeks after the last asparaginase dose and 2 weeks from the start of the last dexamethasone course; TXVI SHR, 2 weeks after the last asparaginase dose and 2 weeks from the start of the last dexamethasone course), week 8 (after full asparaginase and dexamethasone exposure the prior week), and either week 12 (TXV LR, 3 weeks after the last asparaginase dose and 3 weeks from the start of the last dexamethasone course; TXV SHR, 1 week after the last asparaginase dose and 3 weeks

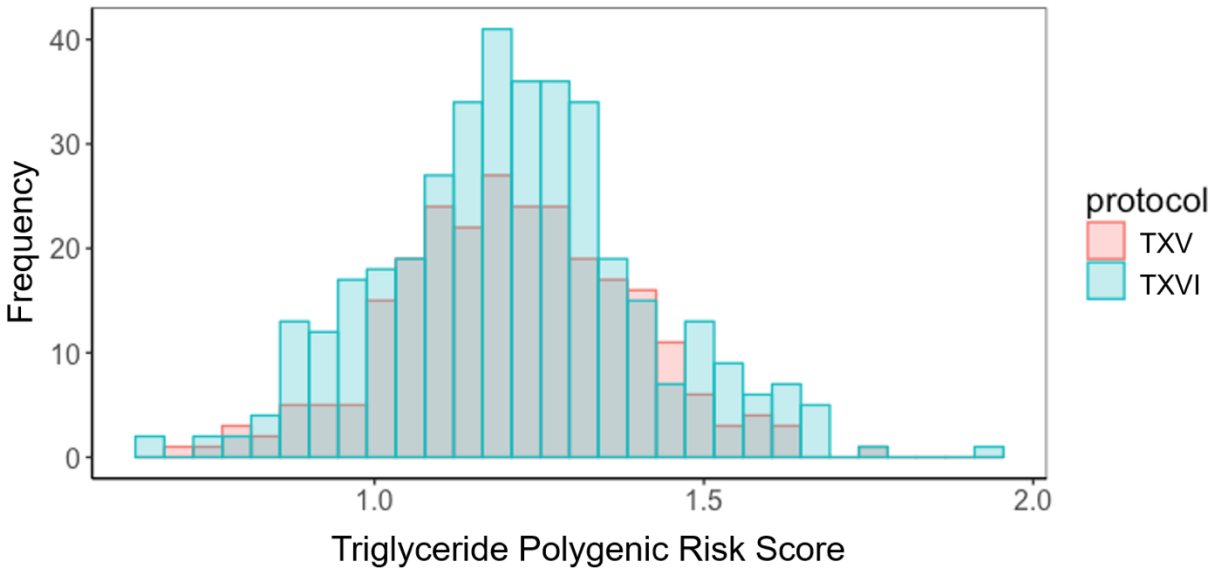
from the start of the last dexamethasone course or week 17 (TXVI LR, 8 weeks after the last asparaginase dose and 3 weeks from the start of the last dexamethasone course; TXVI SHR, 2 weeks after the last asparaginase dose and 3 weeks from the start of the last dexamethasone course) of continuation. The relative dexamethasone dose (DEX) was identical between protocols. In TXV, patients received L-ASP: LR (A) and SHR (C); and in TXVI patients received PEG-ASP: LR (B) and SHR (D). Arrows indicate timing of TG measurements. Red boxes indicate timing of DEX, orange bars indicate timing of ASP. LR= low risk treatment arm, SHR= standard/high risk treatment arm.



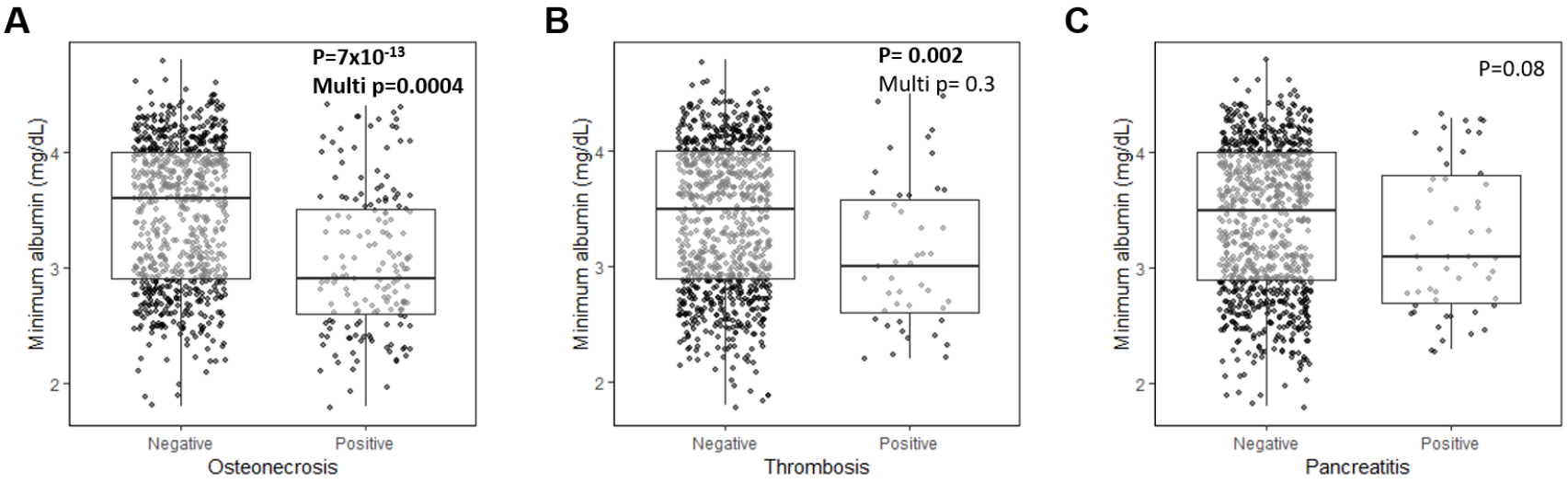
Supporting Information Figure S3: Diagram of patients included in analysis by protocol. TG, triglyceride; SJCRH, St. Jude. Children's Research Hospital. Only patients with ≥ 2 TG measurements were included in single time-point analyses (TXV: n=362; TXVI=563; for longitudinal analyses, only patients with all 4 TG measurements were included (TXV: n=265; TXVI=508).



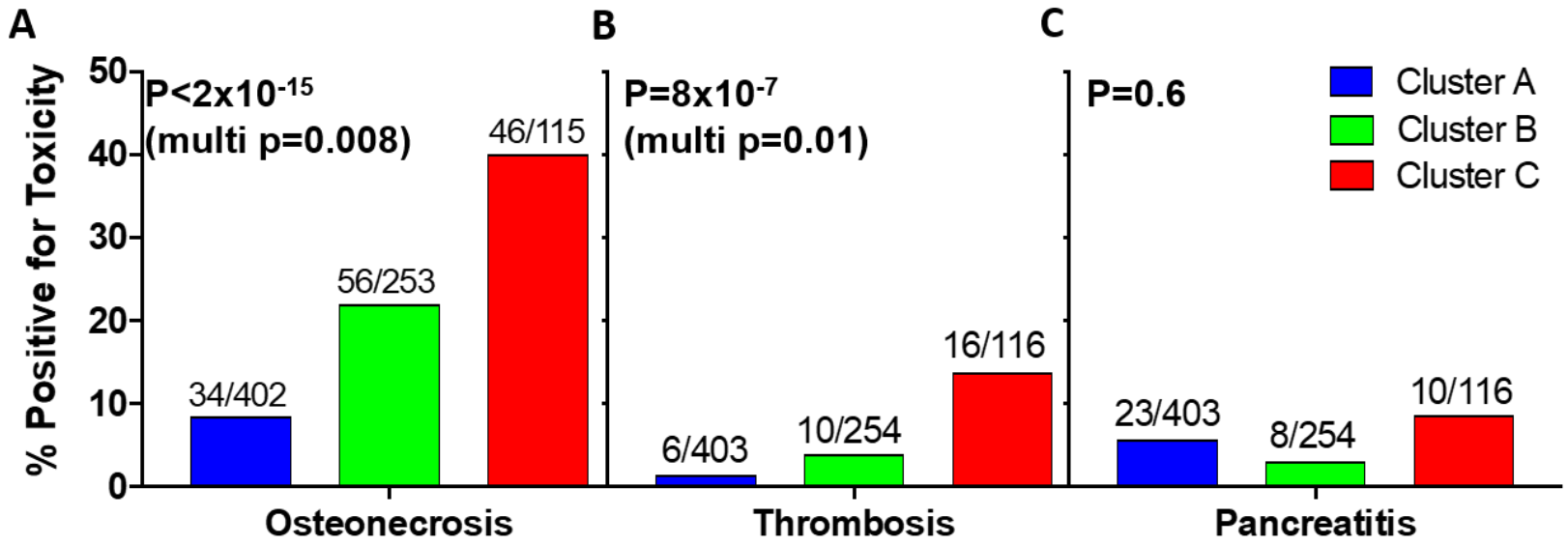
Supporting Information Figure S4: Maximum hypertriglyceridemia grade by PEG-asparaginase dose in TXVI. PEG-asparaginase (PEG-ASP) randomization reflects dose given at week 7 of continuation. A subset of patients switched to *Erwinia* L-asparaginase (*Erwinia*) at or prior to week 7 of continuation. Maximum hypertriglyceridemia (hyperTG) grade occurred at weeks 7, 8, or 17 of continuation therapy. CTCAE v4 was used to define grade of hyperTG. No patients on *Erwinia* developed grade 4 hyperTG. Only patients with at least two lipid measurements were included in analysis. Low Risk: *Erwinia* (n=20), 2500 U/m^2/dose (n=155), 3500 U/m^2/dose (n=80); Standard/High Risk: *Erwinia* (n=46), 2500 U/m^2/dose (n=160), 3500 U/m^2/dose (n=102).



Supporting Information Figure S5: Distribution of triglyceride- polygenic risk score (triglyceride-PRS) in European ancestry patients on TXV and TXVI by protocol. The triglyceride-PRS range was 0.66-1.93. There was no difference in triglyceride-PRS between protocols (p=0.99). n=642 genetically white patients in TXV + TXVI.



Supporting Information Figure S6: Lower serum albumin was associated with symptomatic osteonecrosis (A) and thrombosis (B), but not pancreatitis (C). Minimum observed serum albumin (at week 7 or 8) was compared between patients positive or negative for toxicity. Positive adverse events were grade 2-4 symptomatic osteonecrosis, grade 3-4 thrombosis, or for pancreatitis grade 3-4 (TXV) or grade 2-4 (TXVI). Covariates included in multivariate analyses included age, gender, race, risk-arm, and protocol.



Supporting Information Figure S7: Patients in high-risk cluster C had higher frequency of post-induction osteonecrosis and thrombosis, but not pancreatitis. Adverse events were graded by CTCAE guidelines (TXV: v2; TXVI: v3), with positive grades as: A) symptomatic osteonecrosis grade 2-4; B) thrombosis grade 3-4; and C) pancreatitis grade 3-4 (TXV) or grade 2-4 (TXVI). Adverse events occurred post-remission induction through off therapy follow-up. Age, gender, race, minimum serum albumin, treatment arm, and protocol where covariates in multivariate analyses.

		Grade 1	Grade 2	Grade 3	Grade 4
Osteonecrosis	CTCAE v2/v3	Asymptomatic and detected by imaging only	Symptomatic and interfering with function, but not interfering with ADL; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with ADL; operative intervention or hyperbaric oxygen indicated	Symptomatic; or disabling
Thrombosis	CTCAE v2/v3	-	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) not indicated	Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anticoagulation, lysis, filter, invasive procedure) indicated	Embolic event including pulmonary embolism or life-threatening thrombus
Pancreatitis	CTCAE v2 (TXV)	-	-	Abdominal pain with pancreatic enzyme elevation	Complicated by shock (acute circulatory failure)
	CTCAE v3 (TXVI)	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)

Supporting Information Table S1: Grading of toxicities (osteonecrosis, thrombosis, and pancreatitis) for patients on TXV and TXVI therapy. Adapted from National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 2.0 (v2: TXV therapy) and version 3.0 (v3: TXVI therapy). Shaded boxes indicate grades considered positive for the respective toxicity: symptomatic osteonecrosis grade 2-4; thrombosis grade 3-4; and pancreatitis grade 3-4 (TXV) or grade 2-4 (TXVI).

				Reported		Observed in TXV/TXVI European patients	
Location	**rsID**	**Gene**	**Risk Allele**	**Effect Size**	**p-value**	**Effect Size**	**p-value**
1:63025942	rs2131925	*DOCK7, ANGPTL3*	T	0.066	$3x10^{-74}$	-0.161	0.0078
1:230295691	rs4846914	*GALNT2*	G	0.04	$7x10^{-31}$	-0.033	0.553
4:88030261	rs442177	*KLHL8, AFF1*	T	0.031	$1x10^{-18}$	-0.005	0.862
5:55861786	rs9686661	*MAP3K1, ANKRD55*	T	0.038	$3x10^{-16}$	0.035	0.826
7:72982874	rs17145738	*MLXIPL*	C	0.115	$9x10^{-99}$	-0.185	0.026
8:18272881	rs1495741	*NAT2*	G	0.04	$3x10^{-12}$	0.132	0.052
8:19844222	rs12678919	*LPL*	A	0.17	$2x10^{-199}$	-0.162	0.099
8:126490972	rs2954029	*TRIB1*	A	0.076	$1x10^{-107}$	-0.09	0.127
10:65027610	rs10761731	*JMJD1C*	A	0.031	$8x10^{-12}$	0.038	0.51
11:61569830	rs174546	*FADS1, FADS2, FADS3*	T	0.045	$7x10^{-38}$	0.93	0.153
11:116648917	rs964184	*APOA1, APOC3, APOA4, APOA5*	G	0.234	$7x10^{-224}$	0.373	$4x10^{-6}$
15:42683787	rs2412710	*CAPN3*	A	0.099	$2x10^{-11}$	0.194	0.416
15:44245931	rs2929282	*FRMD5*	T	0.072	$2x10^{-9}$	0.068	0.663
16:56993324	rs3764261	*CETP*	C	0.04	$2x10^{-25}$	0.29	0.755
19:19407718	rs10401969	*CSPG3, CILP2, PBX4*	T	0.121	$1x10^{-69}$	0.099	0.38
20:44554015	rs6065906	*PLTP*	C	0.053	$2x10^{-34}$	0.087	0.277

Supporting Information Table S2: 16 SNPs used to calculate triglyceride polygenic risk score (triglyceride-PRS). These SNPs were associated with increased serum triglycerides in healthy European individuals; SNP information, including the reported risk allele, effect size, and p-value, was extracted from Willer et al., 2013 [6] and Dron et al., 2018 [7] which utilized data from the 1000 Genomes Project [10]. In TXV/TXVI, the observed p-value and effect size were calculated using maximum triglyceride measurement during continuation (at week 7, 8 or 12/17) in white patients (> 90% Northern European ancestry). N=642 for TXV/TXVI.

A

LR, TXV paired Wilcoxon p-values, n=142				
	Baseline	Week 7	Week 8	Week 12
Baseline	-	-	-	-
Week 7	$2x10^{-8}$	-	-	-
Week 8	0.08	**$3x10^{-14}$**	-	-
Week 12	0.7	**$7x10^{-12}$**	0.09	-

B

LR, TXVI paired Wilcoxon p-values, n=229				
	Baseline	Week 7	Week 8	Week 17
Baseline	-	-	-	-
Week 7	$< 1x10^{-15}$	-	-	-
Week 8	**$1x10^{-8}$**	**$< 1x10^{-15}$**	-	-
Week 17	0.1	**$< 1x10^{-15}$**	$6x10^{-11}$	-

C

SHR, TXV paired Wilcoxon p-values, n=123				
	Baseline	Week 7	Week 8	Week 12
Baseline	-	-	-	-
Week 7	**$1x10^{-5}$**	-	-	-
Week 8	**$< 1x10^{-15}$**	**$3x10^{-14}$**	-	-
Week 12	**$9x10^{-9}$**	**$2x10^{-3}$**	$3x10^{-7}$	-

D

SHR, TXVI paired Wilcoxon p-values, n=279				
	Baseline	Week 7	Week 8	Week 17
Baseline	-	-	-	-
Week 7	**$< 1x10^{-15}$**	-	-	-
Week 8	**$< 1x10^{-15}$**	**$< 1x10^{-15}$**	-	-
Week 17	**$< 1x10^{-15}$**	0.3	$< 1x10^{-15}$	-

Increase
Decrease

Supporting Information Table S3: Wilcoxon p-values for intrapatient difference in triglycerides between time points. LR, TXV (A); LR, TXVI (B); SHR, TXV (C); SHR, TXVI (D). The shading of the boxes indicates whether triglycerides were increased (blue) or decreased (pink) relative to baseline. Only relevant comparisons were analyzed.

	Baseline			Week 7			Week 8			Week 12/17		
	TXV	TXVI	p-value	TXV	TXVI	p-value	TXV	TXVI	p-value	TXV	TXVI	p-value
LR, TXV vs. TXVI												
Median TG (interdecile range), mg/dL	90 (39-7-258.2)	96 (44.7-232.4)	0.62	65 (34-164)	63 (33-132)	0.17	102 (50.7-400.8)	119 (48.2-377.8)	0.14	96 (49-212.9)	88 (43-206.8)	**0.04**
n patients TG > 1000 mg/dL/total n patients (%)	0/179 (0%)	0/248 (0%)	n.a.	0/179 (0%)	0/253 (0%)	n.a.	0/175 (0%)	0/245 (0%)	n.a.	0/173 (0%)	0/247 (0%)	n.a.
SHR, TXV vs. TXVI												
Median TG (interdecile range), mg/dL	91.5 (40.9-256.2)	89 (43-204.9)	0.74	133 (53-510.7)	179 (62-1397)	**$8x10^{-7}$**	246 (66-1372)	392 (72-1690.5)	**0.0007**	137.5 (55.6-745.9)	200 (54-1330.5)	**0.008**
n patients TG > 1000 mg/dL/total n patients (%)	0/170 (0%)	1/302 (0.3%)	0.9	2/167 (1.2%)	23/305 (7.5%)	**0.0064**	14/161 (**8.7%**)	46/295 (**15.6%**)	**0.049**	6/154 (3.9%)	22/299 (7.4%)	0.21

Supporting Information Table S4: Differences between protocols (TXV vs. TXVI) by risk-arm (LR or SHR) at four time-points. Triglycerides (TG) were compared by risk-arm and between protocols. Median TG (with interdecile range) are shown for each time point. The number (%) of patients with grade 4 hypertriglyceridemia (>1000 mg/dL: CTCAE v4.0) are shown for each time point. TXVI had more unique patients with at least one occurrence of grade 4 hypertriglyceridemia compared to TXV: 10.5% (59/563) vs. 5.5% (20/362), respectively (p=0.007). Only patients with at least two lipid measurements were included in analysis. TXV, LR (n=189); TXVI, LR (n=255); TXV, SHR (n=173); TXVI, SHR (n=308). At each time point, Wilcoxon tests were used to compare TGs measurements and chi-square tests were used to compare the proportion of cases of grade 4 hypertriglyceridemia.

	TXV, LR	TXVI, LR	TXV, SHR	TXVI, SHR
TXV, LR	-	-	-	-
TXVI, LR	0.36	-	-	-
TXV, SHR	**$< 1x10^{-15}$**	-	-	-
TXVI, SHR	-	**$< 1x10^{-15}$**	**0.0001**	-

Increase

Decrease

Supporting Information Table S5. P-values for association of maximum hypertriglyceridemia grade between protocol and treatment group. P-values were derived using proportional odds models: comparing the hypertriglyceridemia grade between protocol and/or risk arm. The shading of the boxes indicates the direction of the difference between the group on the left relative to the group on the top. Only patients with at least two triglyceride measurements were included. Only relevant comparisons were analyzed.

	LR, 2500	LR, 3500	SHR, 2500	SHR, 3500
LR, 2500	-	-	-	-
LR, 3500	0.22	-	-	-
SHR, 2500	**$< 1x10^{-15}$**	-	-	-
SHR, 3500	-	**$4x10^{-13}$**	0.44	-

Increase
Decrease

Supporting Information Table S6: Maximum hypertriglyceridemia grade was compared between PEG-asparaginase dose (2500 U/m^2/dose vs. 3500 U/m^2/dose) and risk group (LR or SHR) in TXVI using proportional odds models. Only patients that received full PEG-asparaginase (2500 U/m^2 or 3500 U/m^2) dose at week 7 were included. P-values were derived using proportional odds models: comparing the hypertriglyceridemia grade between PEG-asparaginase randomization and/or risk arm. The shading of the boxes indicates the direction of the difference between the group on the left relative to the group on the top. Only patients with at least two triglyceride measurements were included. Only relevant comparisons were analyzed.

Risk Factor		Cluster A n=403 (52%)	Cluster B n=254 (33%)	Cluster C n=116 (15%)	Effect Size (uni)	p-value (uni)	Effect Size (multi)	P-value (multi)
Age at diagnosis	Median (interdecile range), years	4.3 (1.8-14.7)	5.8 (1.4-16.2)	11.4 (2.9-18.5)	**1.12 (1.09-1.14)**	**$<2x10^{-15}$**	**1.07 (1.05-1.08)**	**$4x10^{-6}$**
Gender	Male, n (%)	177 (44%)	115 (45%)	36 (31%)	1.17 (0.96-1.41) (male)	0.1		
	Female, n (%)	226 (56%)	139 (55%)	80 (69%)				
Race	White, n (%)	263 (65%)	194 (77%)	76 (66%)	1.19 (0.96-1.46) (white)	0.09		
	Black, n (%)	70 (18%)	25 (10%)	14 (12%)				
	Hispanic, n (%)	36 (9%)	19 (7%)	14 (12%)				
	Other, n (%)	34 (8%)	16 (6%)	12 (10%)				
BMI	Median (interdecile range), z-score	0.66 (-1.49-2.37)	0.65 (-1.60-2.49)	0.68 (-1.19-2.15)	1.02 (0.93-1.1)	0.7		
Protocol	TXV, n (%)	156 (39%)	84 (33%)	25 (22%)	**1.39 (1.13-1.69) (TXVI)**	**0.001**	1.15 (0.99-1.60)	0.28
	TXVI, n (%)	247 (61%)	170 (67%)	91 (78%)				
Treatment risk arm	LR, n (%)	299 (74%)	72 (28%)	0 (0%)	**6.15 (4.86-7.78) (SHR)**	**$<2x10^{-15}$**	**3.36 (2.42-4.63)**	**$2x10^{-14}$**
	SHR, n (%)	104 (26%)	182 (72%)	116 (100%)				
Minimum serum albumin	Median (interdecile range), mg/dL	3.8 (2.6-4.3)	3.0 (2.3 – 4.2)	2.8 (2.3-3.6)	**0.29 (0.24-0.35)**	**$<2x10^{-15}$**	**0.62 (0.48-0.79)**	**0.0005**
Anti-ASP Antibody	Negative, n (%)	248 (62%)	191 (75%)	95 (82%)	**0.58 (0.53-0.66)**	**$2x10^{-6}$**	0.74 (0.64-0.87)	0.06
	Positive, n (%)	155 (38%)	63 (25%)	21 (18%)				
ASP-RXN	RXN negative, n (%)	286 (71%)	205 (81%)	103 (89%)	**0.59 (0.47-0.75)**	**$9x10^{-6}$**	0.81 (0.69-0.95)	0.2
	RXN positive, n (%)	117 (29%)	49 (19%)	13 (11%)				

Supporting Information Table S7: Univariate and multivariate analyses of risk factors for longitudinal triglyceride cluster. For categorical risk factors, the direction of the relationship with increasing triglyceride cluster (A→B→C) is

indicated. Significant covariates in univariate (uni) analyses were included in a multivariate (multi) proportional odds model. Effect size with 95% CI shown for univariate and multivariate analyses. Minimum serum albumin indicates the lowest observed measurement during continuation (at week 7, 8 or 12/17). Anti-ASP refers to anti-Elspar in TXV and anti-Oncaspar in TXVI (positive patients had detectable antibody at or before week 7).[11] Patients with allergic reaction to front-line asparaginase formulation were considered ASP-RXN positive. Only patients with complete triglyceride measurements were included (n= 773).

Location	rsID	Gene	Risk Allele	Effect Size	p value
14:90646204	rs117897065	KCNK13	G	1.213	$3.9x10^{-7}$
5:78964729	rs10514164	PAPD4	G	1.403	$4.4x10^{-7}$
9:32865569	rs6476383	TMEM215	A	1.04	$8.3x10^{-7}$
1:30783300	rs10915074	MATN1	A	1.6365	$1.8x10^{-6}$
4:153239288	rs17361600	FBXW7	C	0.908	$2.0x10^{-6}$
16:86364054	rs2665324	LOC732275	G	0.275	$2.7x10^{-6}$
3:130132851	rs10512767	COL6A5	G	0.381	$3.1x10^{-6}$
16:84594182	rs62050683	COTL1	G	0.435	$4.1x10^{-6}$
11:116648917	rs964184	APOA1	G	0.373	$4.7x10^{-6}$
11:116611733	rs9326246	BUD13	C	0.503	$4.9x10^{-6}$
2:41698363	rs10166793	LOC388942	A	0.343	$5.0x10^{-6}$
12:25603015	rs11048044	IFLTD1	T	0.445	$5.7x10^{-6}$
8:3844968	rs2627384	CSMD1	G	0.305	$5.7x10^{-6}$
1:157943030	rs143474869	KIRREL	T	1.01	$5.9x10^{-6}$
11:26839277	rs72886798	SLC5A12	T	0.515	$6.6x10^{-6}$
6:164186527	rs79424303	QKI	G	0.549	$6.8x10^{-6}$
8:1848860	rs7013741	ARHGEF10	A	0.388	$7.5x10^{-6}$
3:117141277	rs6797385	LSAMP-AS1	A	0.263	$7.5x10^{-6}$
7:31711890	rs34134	CCDC129	T	1.039	$7.9x10^{-6}$
7:34642091	rs113144554	NPSR1-AS1	A	0.955	$8.7x10^{-6}$

Supporting Information Table S8: Top 20 SNPs associated with maximum triglyceride measurement during continuation European patients in TXV/TXVI. The observed p-value and effect size were calculated using maximum triglyceride measurement during continuation (at week 7, 8 or 12/17) in white patients (>90% Northern European ancestry) and ordered by p-value. N=642 for TXV + TXVI.

Supporting Information References

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