

Supplementary Information

Table S1. Inclusion and exclusion criteria.

Inclusion and Eligibility Criteria	Exclusion and Ineligibility Criteria
- Participant is willing and able to give informed consent for participation in the trial. Adult male or female subjects ≥ 18 years of age who can understand study procedures, comply with them, and provide written informed consent before any study-specific procedure. - Diagnosed with <i>de novo</i> acute myeloid leukaemia or acute lymphoblastic leukaemia. History of cytologically or histologically confirmed diagnosis of AML or ALL (except acute promyelocytic leukemia) according to the 2008 World Health Organisation (WHO) classification (bone marrow [BM] or peripheral blood [PB] blast counts $\geq 20\%$). - Participant is scheduled to undergo induction chemotherapy as an inpatient. - Performance status (Eastern Cooperative Oncology Group; ECOG) of 0-2. - Body mass index (BMI) ≥ 18.5 kg/m² (normal and above) or 16-18.5 kg/m² (underweight) if considered safe by the treating physician and dietician. - Adequate renal function (serum creatinine $< 1.5 \times$ UNL [upper normal limit] or creatinine clearance > 50 mL/min). Creatinine clearance or glomerular filtration rate ≥ 30 mL/min as estimated by the Cockcroft-Gault (C-G) or other medically acceptable formulas, such as MDRD (Modification of Diet in Renal Disease) or CKD-EPI (the Chronic Kidney Disease Epidemiology Collaboration). - Ability to complete the patient booklet by themselves or with assistance. - Ability and willingness to undergo a short-term ketogenic diet combined with short-term fasting prior to and during chemotherapy. - Subjects who are currently receiving prophylaxis antibiotics, prophylaxis antifungal medication and/or prophylaxis antiviral medication.	- Pregnant and/or nursing women. - Patients with type 1 diabetes or patients with type 2 diabetes receiving insulin. - History of syncope with calorie restriction in the past or other medical comorbidities, which would make fasting potentially dangerous. - History of severe heart failure. - Psychiatric conditions that preclude adherence to the study protocol. Known significant mental illness or other condition, such as active alcohol or other substance abuse or addiction that, in the opinion of the investigator, predisposes the subject to high risk of noncompliance with the protocol. - Inability to maintain adequate nutrition and/or patients receiving parenteral nutrition at admission. - Primary carnitine deficiency, carnitine palmitoyl transferase I or II deficiency, carnitine translocase deficiency, beta-oxidation defects, medium-chain acyl dehydrogenase deficiency, long-chain acyl dehydrogenase deficiency, short-chain acyl dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA deficiency, medium-chain 3-hydroxyacyl-CoA deficiency, pyruvate carboxylase deficiency, and porphyria. - Patients with dietary restrictions incompatible with the trial dietary regimens. - Treated with any investigational therapy within 2 weeks of the first dose of study treatment. - Total serum bilirubin $> 2.5 \times$ upper limit of normal (ULN; except for subjects with Gilbert's Syndrome for whom direct bilirubin is $< 2.5 \times$ ULN), or liver cirrhosis, or chronic liver disease Child-Pugh Class B or C. - Refractory congestive heart failure unresponsive to medical treatment; active infection resistant to all antibiotics; or non-AML-associated pulmonary disease requiring > 2 litres per minute (LPM) oxygen, or any other condition that puts the subject at an imminent risk of death.

Figure S1. CONSORT Flow Diagram.

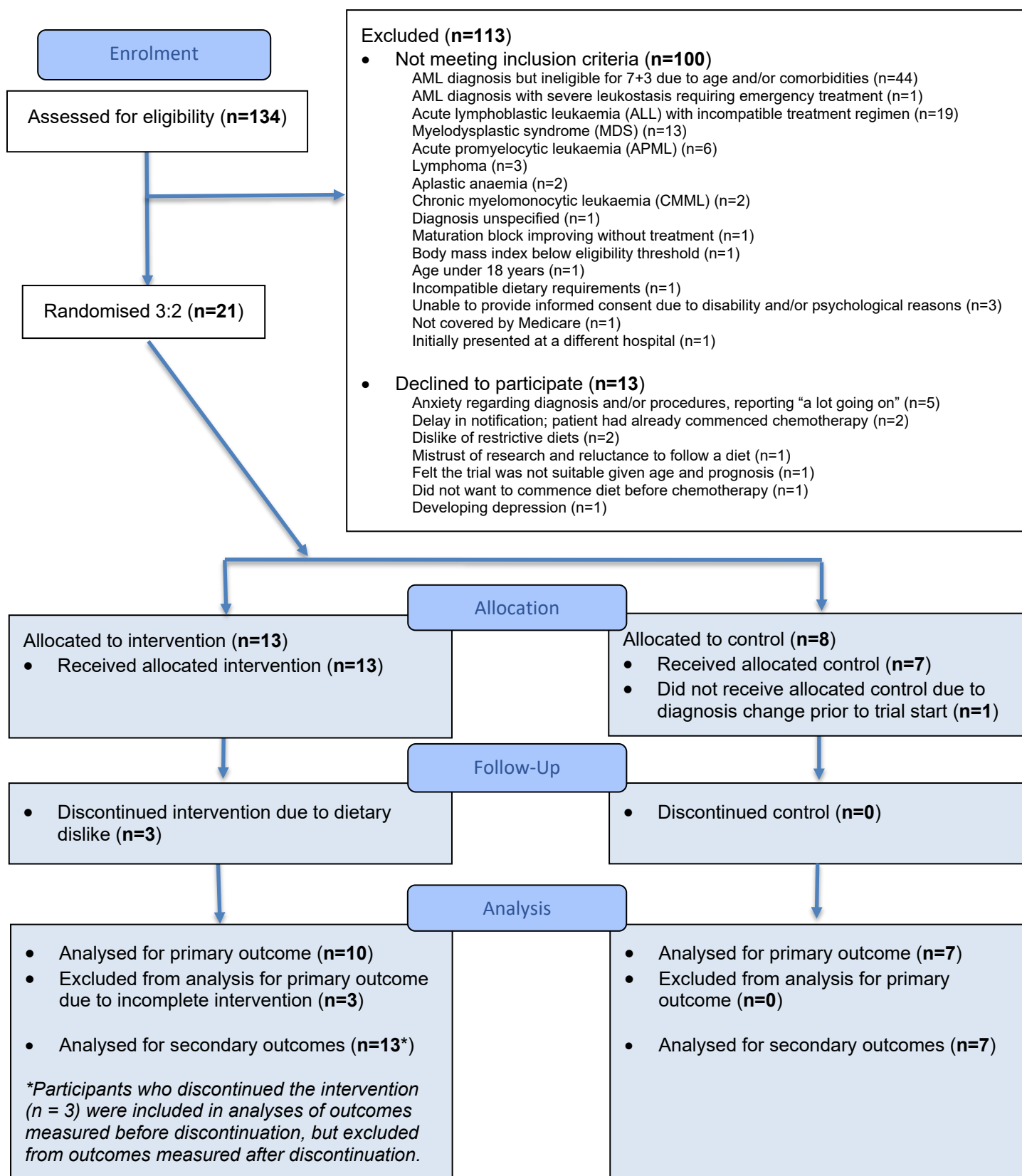


Table S2. Macronutrient composition for the ketogenic intervention.

Hospital Ketogenic Weekly Menu	Energy		Protein			Fat			CHO		
	KJ	Kcal	Gram	Kcal	% Energy	Gram	Kcal	% Energy	Gram	Kcal	% Energy
Day 1	6,947	1,660	55.9	223.6	13.5%	140.0	1260.0	75.9%	43.2	172.8	10.4%
Day 2	6,963	1,664	75.3	301.2	18.1%	139.3	1253.7	75.3%	26.1	104.4	6.3%
Day 3	8,530	2,039	44.0	176.0	8.6%	196.1	1764.9	86.6%	23.6	94.4	4.6%
Day 4	8,624	2,061	53.5	214.0	10.4%	188.4	1695.6	82.3%	37.9	151.6	7.4%
Day 5	9,935	2,375	69.4	277.6	11.7%	222.8	2005.2	84.4%	22.0	88.0	3.7%
Day 6	6,224	1,488	48.0	192.0	12.9%	130.7	1176.3	79.1%	27.2	108.8	7.3%
Day 7	9,046	2,162	60.0	240.0	11.1%	200.3	1802.7	83.4%	29.3	117.2	5.4%
Daily Average	8,038	1,921	58.0	232.1	12.1%	173.9	1565.5	81.5%	29.9	119.6	6.2%
Complementary Ketogenic Snacks	Energy		Protein			Fat			CHO		
	KJ	Kcal	Gram	Kcal	% Energy	Gram	Kcal	% Energy	Gram	Kcal	% Energy
Snack 1: Almond Vanilla Low Carb Bar	686	164	5.2	20.8	12.7%	12.6	113.4	69.2%	2.5	10.0	6.1%
Snack 2: Low Carb Peanut Bar	589	141	7.6	30.4	21.6%	8.0	72.0	51.1%	2.0	8.0	5.7%
Snack 3: Almond Chip Bar	306	73	1.3	5.2	7.1%	6.6	59.4	81.2%	0.6	2.4	3.3%
Snack 4: Keto Granola	1320	315	8.9	35.6	11.3%	27.1	243.9	77.3%	5.1	20.4	6.5%
Snack 5: Crispy Cauliflower Bites	757	181	2.7	10.8	6.0%	15.6	140.4	77.6%	3.6	14.4	8.0%
Snack 6: Atkins Chocolate Coated Almonds	627	150	2.6	10.4	6.9%	11.7	105.3	70.3%	2.4	9.6	6.4%
Snack 7: Smoked Almonds	773	185	6.4	25.6	13.9%	16.5	148.5	80.4%	1.5	6.0	3.2%
Snack 8: Meat Bites & Cheddar Cheese	715	171	9.4	37.6	22.0%	14.7	132.3	77.4%	1.0	4.0	2.3%
Snack 9: Keto Thai Green Chicken Curry	1050	251	25.0	100.0	39.8%	10.0	90.0	35.9%	12.0	48.0	19.1%
Snack 10: Atkins Low Carb Protein Shake	626	150	15.0	60.0	40.1%	9.2	82.8	55.3%	1.0	4.0	2.7%
Average per Snack	745	178	8.4	33.6	18.1%	13.2	118.8	67.6%	3.2	12.7	6.3%
Daily Average (2-3 snacks/day)	1,862.3	445.1	21.0	84.1	-	33.0	297.0	-	7.9	31.7	-
Total Daily Average (Menu + Snacks)	9,900.7	2,366.3	79.0	316.2	13.4%	206.9	1,862.5	78.7%	37.8	151.3	6.4%

Macronutrient energy contributions were calculated using standard Atwater factors (protein and carbohydrate = 4 kcal/g; fat = 9 kcal/g). Percent energy contributions do not sum to exactly 100% due to rounding, exclusion of dietary fibre and sugar alcohols (common in ketogenic products), and minor contributions from non-macronutrient energy sources present in processed ketogenic foods. The diet meets ketogenic targets: <10% of energy from CHO, <50 g/day of CHO, and very high fat content (~80 %).

Table S3. Hospital Ketogenic Weekly Menu.

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast
Ham & Cheese Bake	Plain Omelette	Poached Eggs	Keto Scrambled Eggs & Bacon	Scrambled Eggs	Poached Eggs	Scrambled Eggs
Mashed Pumpkin	Chicken Breast Slice	Hollandaise Sauce	Mashed Pumpkin	Chicken Breast Slice	Carrots	Chicken Breast Slice
Butter	Cheese Tasty Slices	Avocado Pulp	Cheese Tasty Slices	Avocado Pulp	Hollandaise Sauce	Avocado Pulp
	Butter	Ham	Butter	Hollandaise Sauce	Ham	Mashed Pumpkin
Tea or coffee with cream	Tea or coffee with cream	Tea or coffee with cream	Tea or coffee with cream	Tea or coffee with cream	Tea or coffee with cream	Tea or coffee with cream
Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	Lunch
Pork Steak	Roast Lamb	Lamb & Avocado Salad	Chicken Casserole	Cheese & Avocado Salad	Poached Fish and Lemon	Lamb & Avocado Salad
Orange	Carrots	Chicken clear soup	Hollandaise Sauce	Chicken Breast Slice	Hollandaise Sauce	Chicken clear soup
Butter	Avocado Pulp	Cheese Tasty Slices	Avocado Pulp	Mayonnaise	Avocado Pulp	Cheese Tasty Slices
	Mayonnaise	Mayonnaise	Mashed Pumpkin	Butter	Carrot, Zucchini & Tomato	Mayonnaise
Diet Jelly	Diet Jelly	Diet Jelly	Diet Jelly	Diet Jelly	Diet Jelly	Diet Jelly
Lemonade Diet	Lemonade Diet	Lemonade Diet	Lemonade Diet	Lemonade Diet	Lemonade Diet	Lemonade Diet
Afternoon tea	Afternoon tea	Afternoon tea	Afternoon tea	Afternoon tea	Afternoon tea	Afternoon tea
Diet Cordial	Diet Cordial	Diet Cordial	Diet Cordial	Diet Cordial	Diet Cordial	Diet Cordial
Tea or coffee with cream	Tea or coffee with cream	Tea or coffee with cream	Tea or coffee with cream	Tea or coffee with cream	Tea or coffee with cream	Tea or coffee with cream
Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner
Mayonnaise	Chicken & Hollandaise Sauce	Keto Beef Bolognaise	Fish with Hollandaise Sauce	Roast Lamb	Pork Steak	Feta & Spinach Omelette
Carrots	Mashed Pumpkin	Cheese Tasty Slices	Mashed Pumpkin	Hollandaise Sauce	Ketogenic Mashed Potato	Hollandaise Sauce
Grilled Sausages	Ketogenic Mashed Potato	Broccoli	Butter	Avocado Pulp	Mashed Pumpkin	Avocado Pulp
Hollandaise Sauce	Beef or chicken clear soup	Chicken clear soup	Carrots	Carrots	Butter	Any Flavoured Clear Soup
Clear Soup Beef			Clear Soup Beef	Any Flavoured Clear Soup	Chicken clear soup	
Complementary Ketogenic Snacks						
Additional ketogenic snacks and meals were provided, with participants encouraged to consume at least 2–3 snacks per day as needed to maintain energy intake. Snacks were available 24/7 and included a wide range of ketogenic options such as roasted and smoked nuts, ketogenic bars, granola and cereals, fried cauliflower bites, ketogenic chocolate and sweets, frozen ketogenic meals, protein shakes, coconut-based ketogenic yogurt, ketogenic ice cream, and small portions of fresh berries.						

Table S4. Individual intervention windows.

ID	Arm	day -6	day -5	day -4	day -3	day -2	day -1	Induction chemotherapy window							day 8
								day 1	day 2	day 3	day 4	day 5	day 6	day 7	
1	C					Start									End
2	C					Start									End
3	C				Start										End
4	C					Start									End
5	KD			Start				Early termination							
6	KD			Start											End
7	KD			Start											End
8	KD				Start										End
9	C	Did not start													
10	KD				Start										End
11	C							Start							End
12	KD						Start								End
13	KD				Start										End
14	KD					Start									End
15	KD						Start								End
16	KD	Start									Early termination				
17	KD					Start				Early termination					
18	KD						Start								End
19	C				Start										End
20	KD			Start											End
21	C							Start							End

Mean duration KD: 8.7 ± 2.3 days
C = Control, KD = Ketogenic Diet

Figure S2. Quality control for PBMC proteomics. Dimensionality reduction (PCA and MDS) showed no outliers. Note Patient ID 20 was analysed in duplicates (20_BL, 20_PRE, 20_CHE, 20_BL_rp, 20_PRE_rp, 20_CHE_rp) and the duplicate samples clustered closely.



Figure S3. Related to Fig. 2B (larger font). Volcano plot of chemotherapy-induced proteome changes (n=57 samples, three timepoints); up = red, down = blue; longitudinal mixed models with within-group comparison (baseline vs chemotherapy), FDR<0.05.

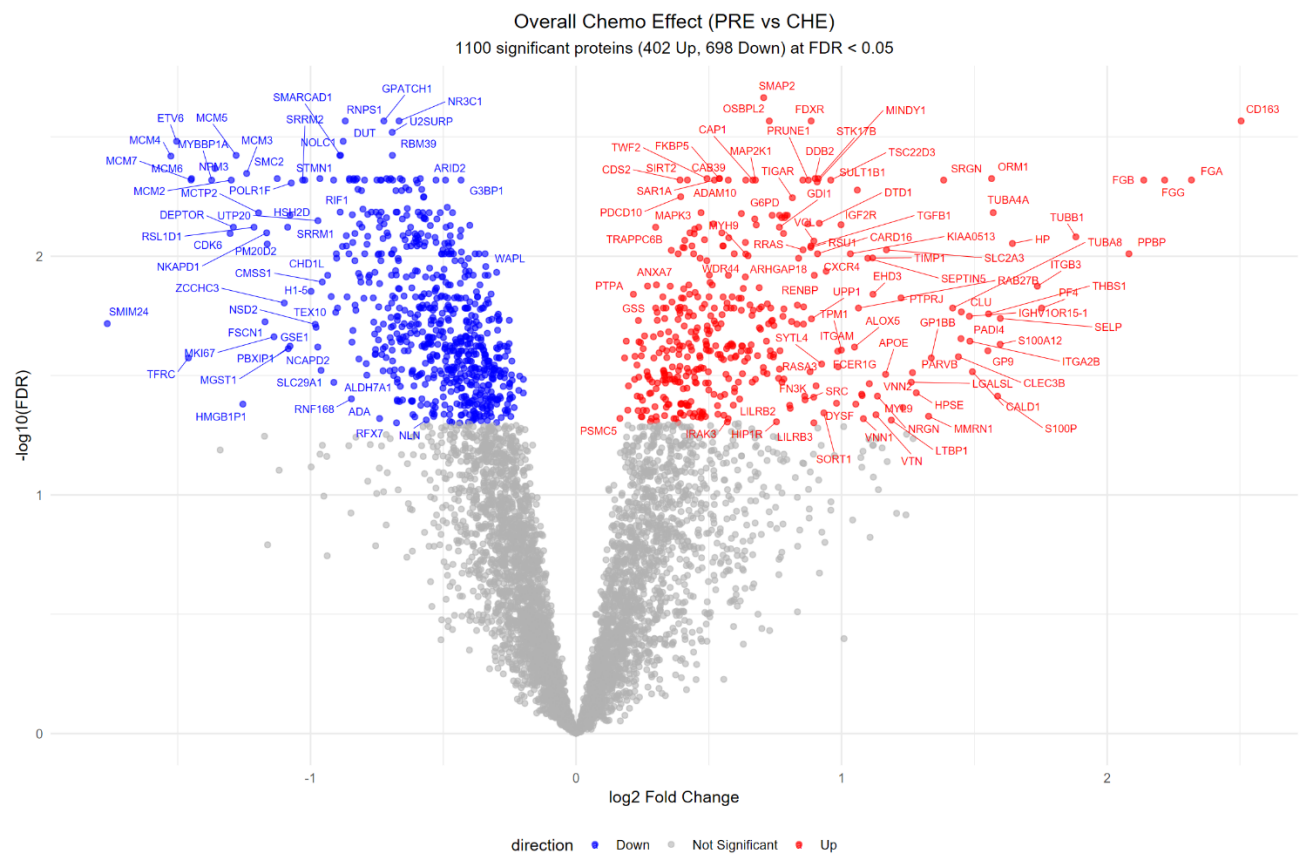
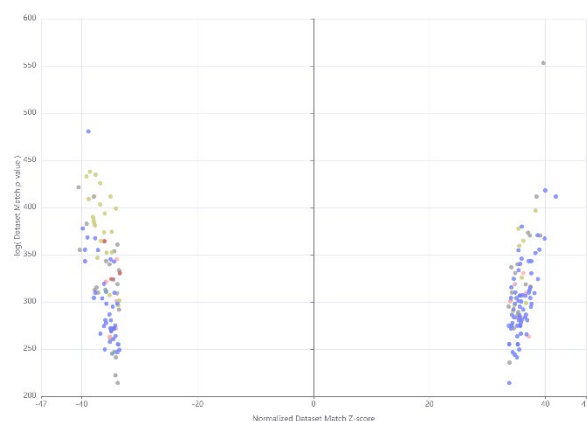
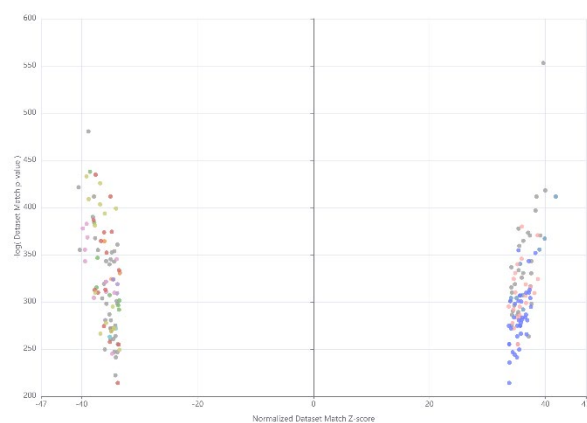


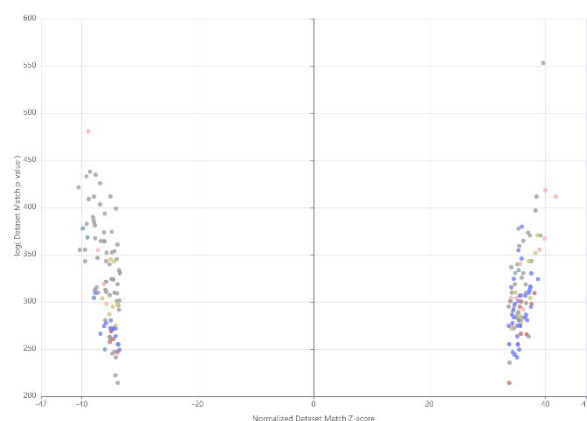
Figure S4. Ingenuity Pathway Analysis: Similarity Analysis of Overall chemotherapy effect (both groups). 1100 significant proteins (402 up, 698 down) FDR < 0.05. Similarity Analysis by Disease (top), Cell type (middle), and Treatment (bottom).



Term	P-value ▲
● acute myeloid leukemia (LAML)	7.18e-120
● autoimmune disease;genetic disease;systemic lupus erythematosus (SLE)	4.61e-64
● monoclonal gammopathy of uncertain significance;multiple myeloma;normal control;smoldering multiple myeloma	3.07e-20
● disease control;osteoarthritis (OA);osteopenia;osteoarthritis (OA);osteoporosis	5.71e-7
● polycythemia vera	3.45e-5
● osteoarthritis (OA);osteoporosis	1.03e-3



Term	P-value ▲
● CD16+ monocyte	2.47e-44
● common lymphoid progenitor (CLP)	2.18e-19
● monocyte	2.67e-17
● hematopoietic stem cell (HSC)	4.02e-16
● macrophage;monocyte	1.50e-15
● hematopoietic precursor cell	4.15e-13
● megakaryocyte-erythroid-mast cell progenitor	3.39e-7
● immature neutrophil	7.95e-7
● erythroid cell	1.37e-5
● endothelial progenitor cell (EPC)	1.56e-5



Term	P-value ▲
● bortezomib;cytarabine;daunorubicin hydrochloride;etoposide	2.43e-38
● cytarabine;daunorubicin hydrochloride;etoposide;sorafenib	1.64e-22
● remission induction therapy	1.20e-15
● bortezomib;cytarabine;daunorubicin hydrochloride;etoposide;cytarabine;daunorubicin hydrochloride;etoposide;sorafenib	8.13e-12
● initial remission induction therapy	3.07e-4

Figure S5. Ingenuity Pathway Analysis of Canonical Pathways: Overall chemotherapy effect (both groups). 1100 significant proteins (402 up, 698 down) FDR < 0.05.



Figure S6. Ingenuity Pathway Analysis: Predictive Activation Analysis of the Overall chemotherapy effect (both groups). 1100 significant proteins (402 up, 698 down) FDR < 0.05. Predictive Activation networks for PTEN, CDKN2A, and CDKN1A.

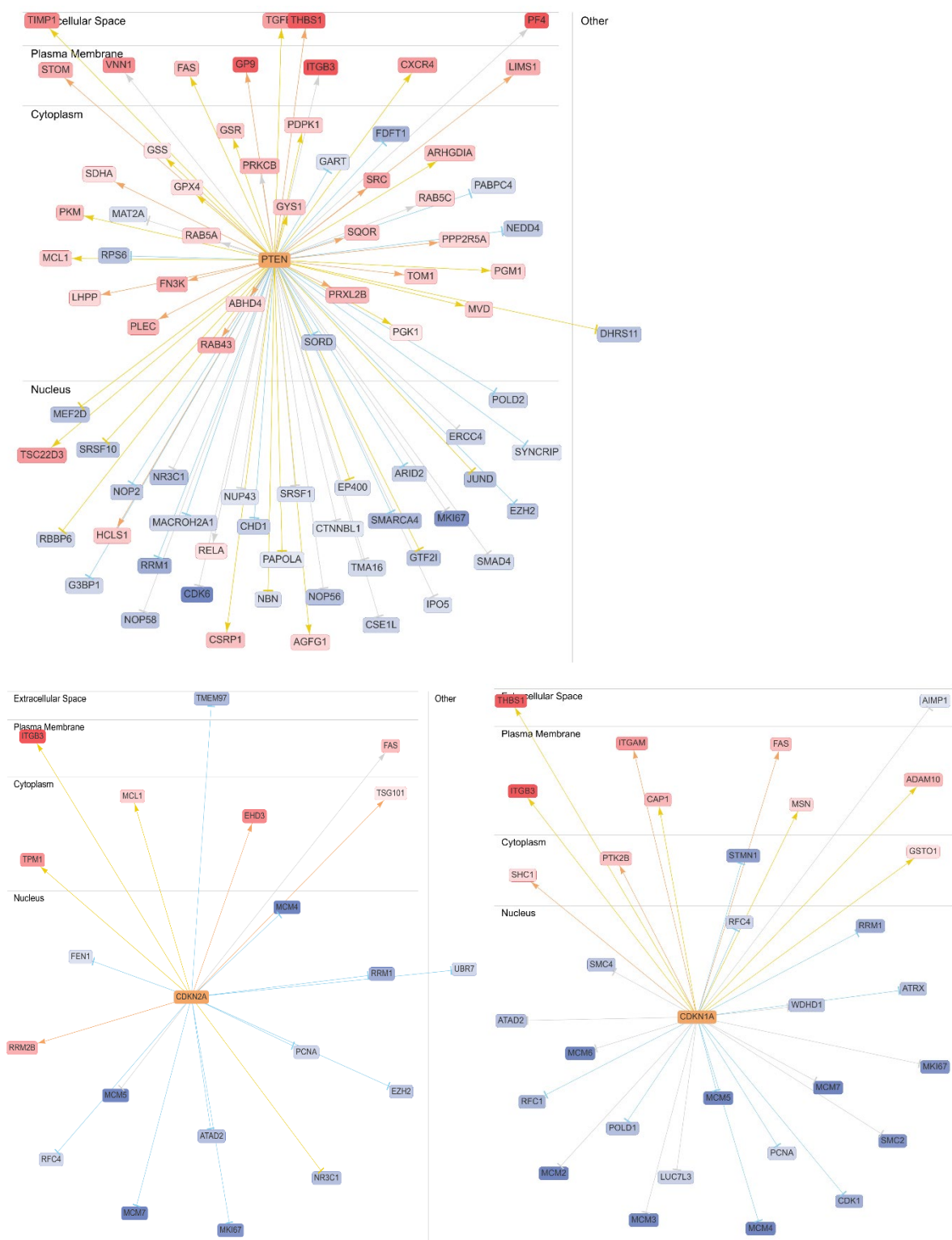


Figure S7. Ingenuity Pathway Analysis: Predictive Activation Analysis. Ketogenic effect during chemotherapy (KD vs Control). 329 significant proteins (231 up, 98 down) FDR < 0.05. Predicted Inhibition (blue) of Translation of Protein. Predicted Activation (orange) of Lipolysis, Hydrolysis of Lipid, and Hydrolysis of Sphingolipids.



Figure S8. Marker-gene validation was performed after removing unassigned cells. To make the algorithm computation tractable, 10% of the cells (200,000 cells) were used to identify markers with FindAllMarkers. The top 10 markers per cluster (filtered to $\text{avg_log2FC} > 1$) are presented in the table below.

GMP-like	MPO	HSC-like	SHANK3	Mono-like	NCF1
GMP-like	MAN1A1	HSC-like	BAALC	Mono-like	STAB1
GMP-like	EGR1	HSC-like	CD34	Mono-like	CD14
GMP-like	ELANE	HSC-like	CD82	Mono-like	GRN
GMP-like	FNDC3B	HSC-like	PROM1	Mono-like	PLXNB2
GMP-like	CDK6	HSC-like	MAN1A1	Mono-like	SLC16A3
GMP-like	RUNX1T1	HSC-like	MSI2	Mono-like	PLAUR
GMP-like	TKT	HSC-like	ERG	Mono-like	TYMP
GMP-like	ETV6	HSC-like	IGF2BP2	Mono-like	TREM1
GMP-like	TUBB	HSC-like	MYB	Mono-like	ALOX5

ProMono-like	HSPA5	Prog-like	CD82	cDC-like	ITGAX
ProMono-like	GRN	Prog-like	SHANK3	cDC-like	GRN
ProMono-like	CAT	Prog-like	CDK6	cDC-like	SAMHD1
ProMono-like	CTSG	Prog-like	MYB	cDC-like	PLXNB2
ProMono-like	IL17RA	Prog-like	PROM1	cDC-like	CIITA
ProMono-like	SCPEP1	Prog-like	TUBB	cDC-like	CFP
ProMono-like	STAB1	Prog-like	CD34	cDC-like	PLAUR
ProMono-like	CCL23	Prog-like	ERG	cDC-like	PAK1
ProMono-like	PRLR	Prog-like	IGF2BP2	cDC-like	CD1D
ProMono-like	EGR1	Prog-like	CAT	cDC-like	IL13RA1

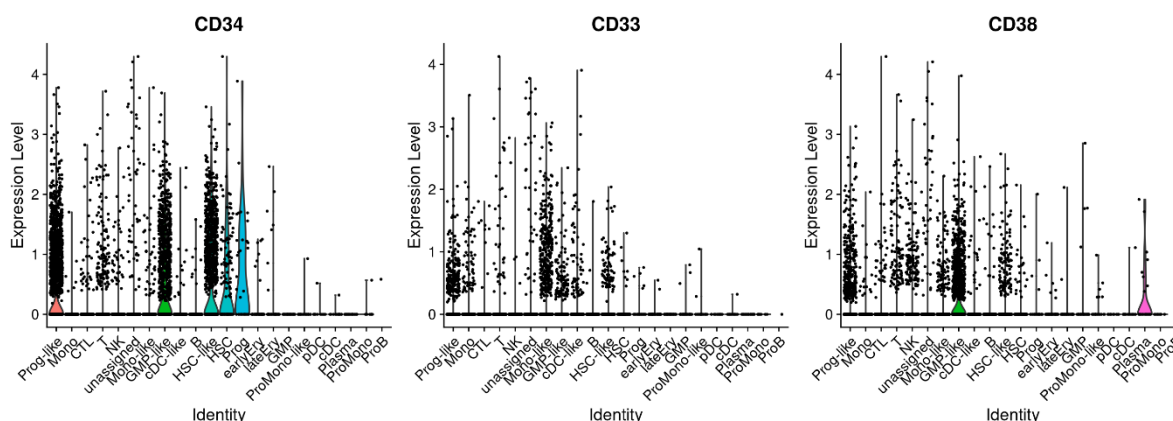


Figure S9. Single cell clustering showing malignant-like populations including HSC-like (110,708 cells; 5.4%), progenitor-like (200,355 cells; 9.8%), GMP-like (110,899 cells; 5.4%), promonocyte-like (3,984 cells; 0.2%), monocyte-like (319,695 cells; 15.6%), and cDC-like (63,226 cells; 3.1%), alongside ~60% non-malignant hematopoietic populations.

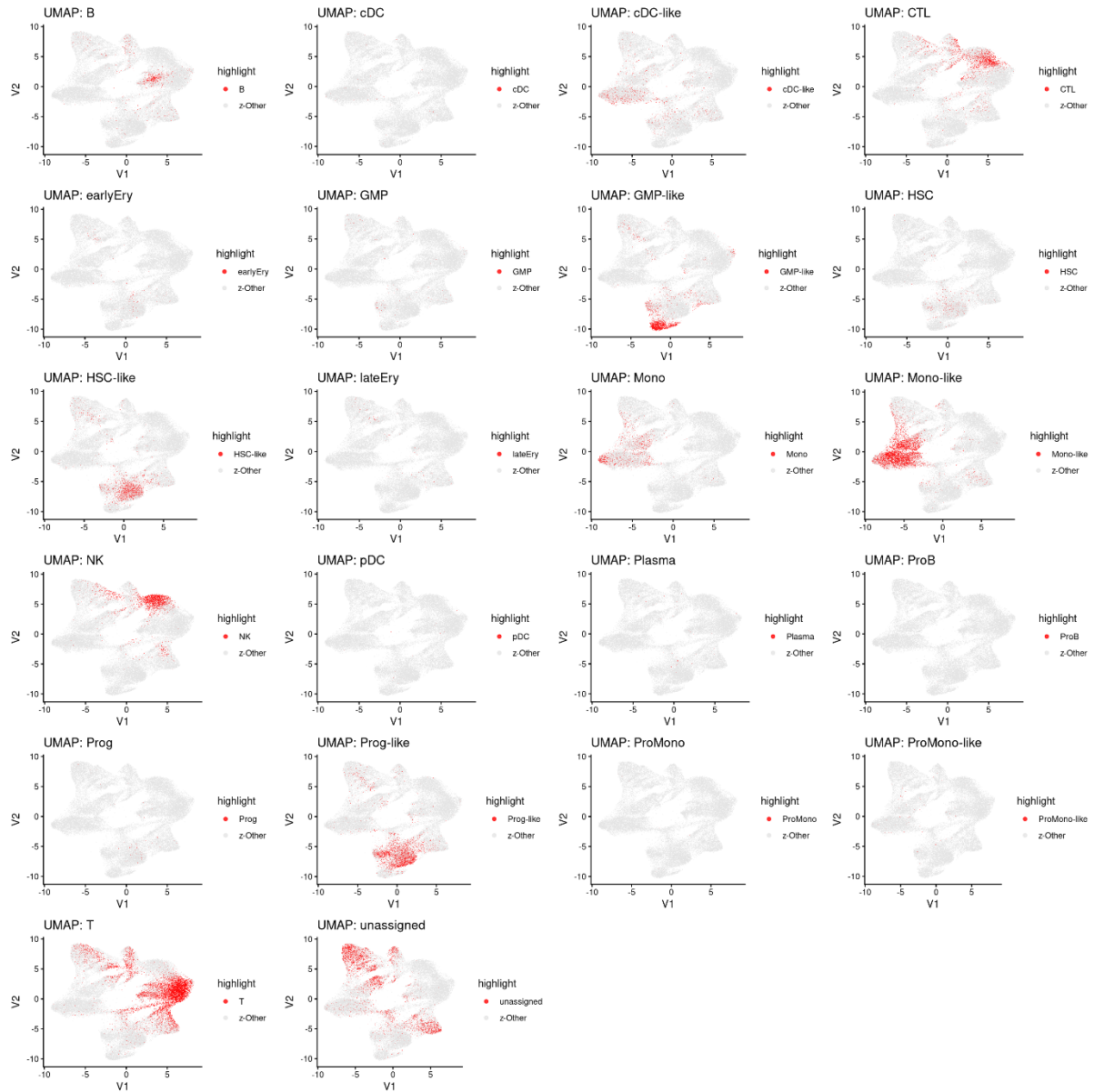


Figure S10. Cell type specific differential transcriptomic analysis of malignant populations, shown as volcano plots for HSC-like, ProMonocyte-like, Progenitor-like, Monocyte-like, GMP-like, and cDC-like cells, with downstream pathway/regulator analysis showing increased fatty acid metabolism and decreased protein metabolism in monocyte-like cells. Repeated-measures mixed-effects models, capturing diet x chemotherapy interactions.

