Supplementary Data

Increased serum cholesterol and long-chain fatty acid levels are associated with the efficacy of nivolumab in patients with non-small-cell lung cancer

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Supplementary Data

Supplementary Methods: Selection of lipids for multiple-lipid analysis.

LDL-cholesterol, HDL-cholesterol, total cholesterol, lauric acid, myristic acid, myristoleic acid, stearic acid, linoleic acid, eicosenoic acid, eicosadienoic acid, and dihomo-γ-linolenic acid were significantly associated with progression-free survival ($P < 0.100$) in univariate Cox proportional hazards analysis (Table 1). Meanwhile, LDL-cholesterol, HDL-cholesterol, total cholesterol, myristic acid, myristoleic acid, stearic acid, linoleic acid, eicosadienoic acid, and dihomo-γ-linolenic acid, behenic acid, and lignoceric acid were significantly associated with overall survival ($P < 0.100$) in univariate Cox proportional hazards analysis (Table 3). Among them, LDL-cholesterol was strongly correlated (Pearson correlation coefficient > 0.70) with total cholesterol and linoleic acid; total cholesterol was strongly correlated with linoleic acid, behenic acid, and lignoceric acid; myristic acid was strongly correlated with myristoleic acid; stearic acid was strongly correlated with linoleic acid, myristic acid, and eicosadienoic acid; linoleic acid was strongly correlated with stearic acid, eicosadienoic acid, behenic acid, and lignoceric acid' behenic acid was strongly correlated with lignoceric acid; and eicosadienoic acid was strongly correlated with dihomo-γ-linolenic acid (Supplementary Table 3). Lipids lacking strong correlations with each other were grouped as follows:

PFS:

Combination A: LDL-cholesterol, HDL-cholesterol, lauric acid, stearic acid, myristoleic acid, eicosenoic acid, and dihomo-γ-linolenic acid (AIC = 1022.5)

Combination B: total cholesterol, HDL-cholesterol, lauric acid, stearic acid, myristoleic acid, eicosenoic acid, and dihomo-γ-linolenic acid (AIC = 1031.7)

Combination C: HDL-cholesterol, lauric acid, myristic acid, eicosenoic acid, and dihomo-γ-linolenic acid (AIC = 1030.5);

Combination D: HDL-cholesterol, lauric acid, myristoleic acid, eicosenoic acid, and dihomo-γ-linolenic acid (AIC = 1030.1)

Combination A had the smallest AIC, and it was selected as the representative combination (Table 2). The results for Combinations B–D are presented in Supplementary Table 5.

OS:

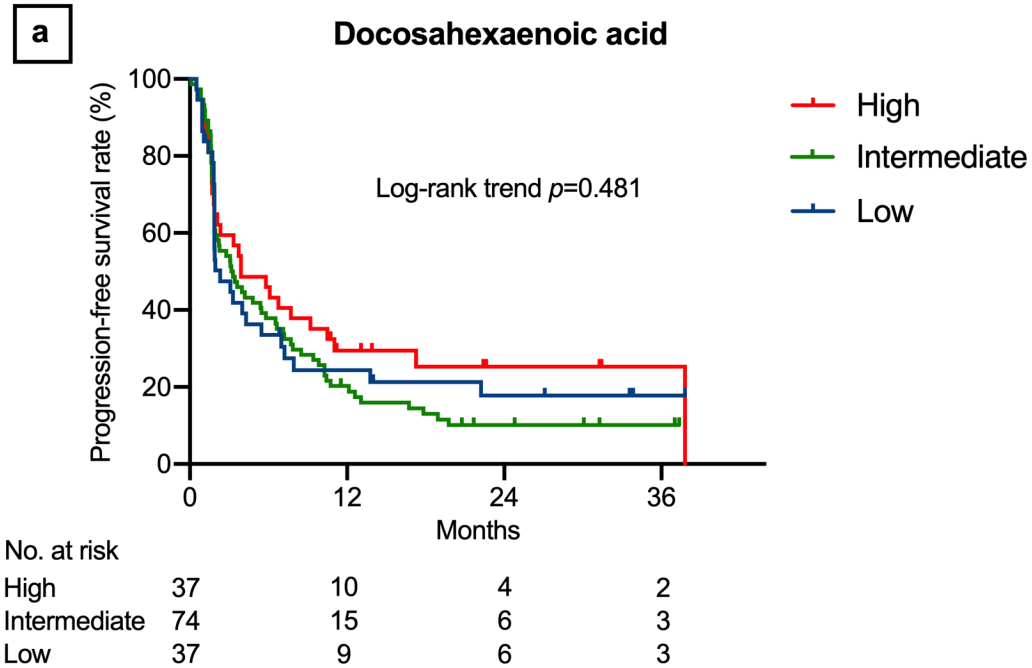
Combination A: LDL-cholesterol, HDL-cholesterol, myristoleic acid, stearic acid, dihomo-γ-linolenic acid, and lignoceric acid (AIC = 769.2)

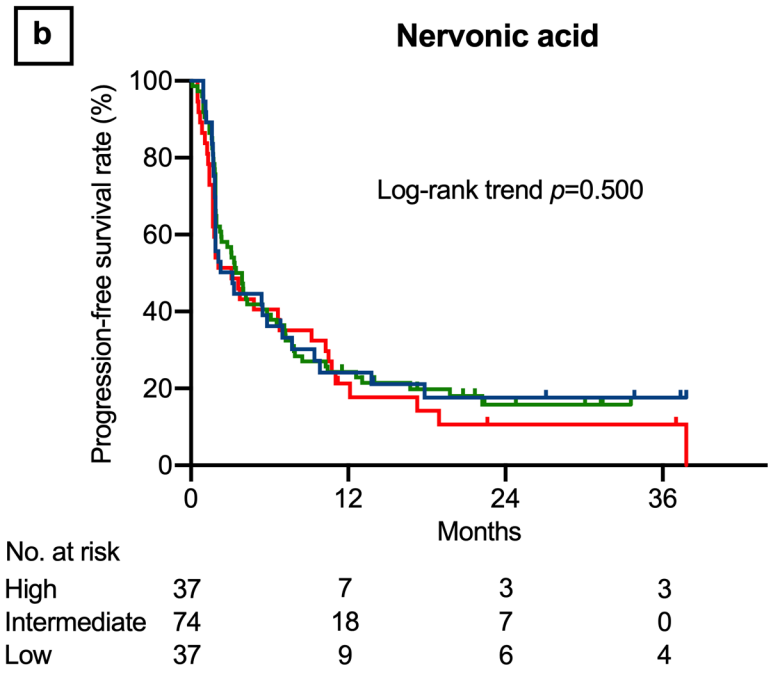
Combination B: LDL-cholesterol, HDL-cholesterol, myristoleic acid, stearic acid, dihomo-γ-linolenic acid, and behenic acid (AIC = 769.3)

Combination C: LDL-cholesterol, HDL-cholesterol, myristic acid, eicosadienoic acid, and lignoceric acid (AIC = 769.9)
Combination D: LDL-cholesterol, HDL-cholesterol, myristoleic acid, eicosadienoic acid, and lignoceric acid (AIC = 769.9)
Combination E: LDL-cholesterol, HDL-cholesterol, myristic acid, eicosadienoic acid, and behenic acid (AIC = 769.2)
Combination F: LDL-cholesterol, HDL-cholesterol, myristoleic acid, eicosadienoic acid, and behenic acid (AIC = 769.9)
Combination G: total cholesterol, HDL-cholesterol, stearic acid, myristoleic acid, and dihomo-γ-linolenic acid (AIC = 775.8)
Combination H: total cholesterol, HDL-cholesterol, myristic acid, and eicosadienoic acid (AIC = 774.0)
Combination I: total cholesterol, HDL-cholesterol, myristoleic acid, and eicosadienoic acid (AIC = 774.0)

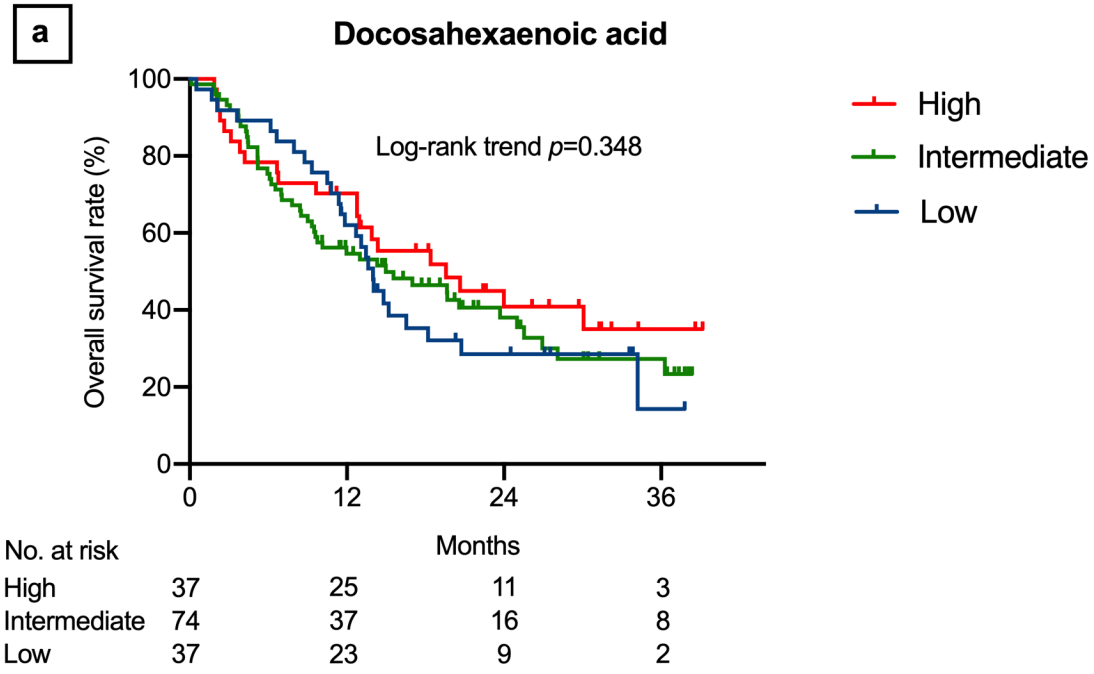
Combination A had the smallest AIC, and it was selected as the representative combination (Table 3). The results for Combinations B–D are presented in Supplementary Table 7.

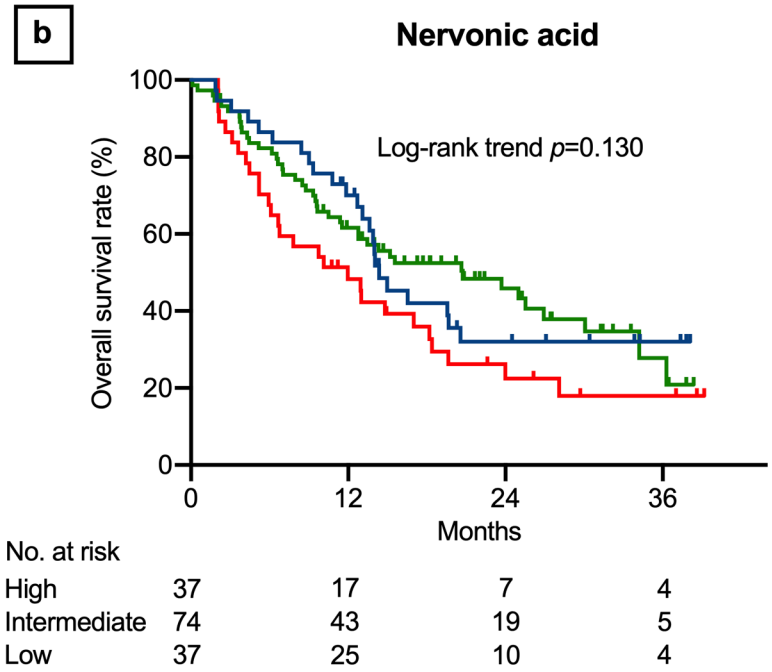
Supplementary Figure 1. Progression-free survival after nivolumab therapy according to serum lipid levels (supplement to Figure 1-4).





Supplementary Figure 2. Overall survival after nivolumab therapy according to serum lipid levels (supplement to Figure 5-8).





Supplementary Data

Supplementary Table 1. Difference in lipid levels between the sexes

Variables	All patients, n=148	Men, n=122	Women, n=26	*p*-value
LDL-cholesterol	85.0 (66.0 – 110.0)	82.0 (64.0 − 108.0)	106.0 (84.8 − 124.0)	0.005
HDL-cholesterol	44.0 (38.0 – 51.8)	43.0 (36.8 − 50.3)	49.0 (43.0 − 56.5)	0.006
Total cholesterol	182.0 (147.3 – 206.0)	178.5 (144.8 − 204.0)	199.0 (174.5 − 249.3)	0.001
Lauric acid	2.2 (1.2 – 4.0)	2.0 (1.2 − 4.0)	2.9 (1.7 − 4.5)	0.807
Myristic acid	21.1 (15.2 – 37.2)	21.4 (13.7 − 33.6)	32.8 (17.8 − 50.7)	0.042
Myristoleic acid	1.4 (0.8 – 2.7)	1.2 (0.8 − 2.5)	1.9 (1.1 − 3.2)	0.081
Palmitic acid	687.4 (568.9 –825.6)	674.9 (548.5 − 816.2)	751.7 (629.9 − 995.0)	0.008
Palmitoleic acid	63.1 (45.9 – 82.8)	61.9 (42.8 − 81.6)	68.1 (49.6 − 90.9)	0.098
Stearic acid	210.9 (173.4 – 252.0)	202.6 (169.2 − 237.2)	241.8 (209.9 − 306.2)	0.001
Oleic acid	621.7 (502.4 – 790.4)	602.3 (487.0 − 780.0)	666.5 (577.1 – 970.3)	0.014
Linoleic acid	755.2 (619.8 – 960.8)	738.5 (602.7 − 934.3)	907.9 (733.6 − 1108.3)	<0.001
γ-linolenic acid	7.1 (4.8 – 10.4)	6.8 (4.7 − 10.0)	8.5 (6.6 − 14.6)	0.007
Linolenic acid	20.4 (15.0 – 32.6)	19.1 (14.3 − 30.1)	30.0 (20.2 − 44.9)	<0.001
Arachidic acid	7.9 (6.4 – 9.8)	7.7 (6.2 − 9.6)	8.6 (7.2 − 11.2)	0.017
Eicosenoic acid	4.9 (3.9 – 6.6)	4.9 (3.9 − 6.2)	4.9 (4.0 − 7.0)	0.094
Eicosadienoic acid	6.5 (5.3 – 8.2)	6.4 (5.3 − 7.8)	7.5 (5.8 − 9.4)	0.016
Eicosatrienoic acid	2.1 (1.6 – 3.5)	2.1 (1.6 − 3.4)	2.5 (1.7 − 3.9)	0.496
Dihomo-γ-linolenic acid	35.1 (27.3 – 43.2)	33.9 (26.5 − 42.6)	37.5 (33.6 − 53.0)	0.079
Arachidonic acid	181.1 (144.7 – 207.1)	175.8 (142.2 − 206.4)	186.6 (172.0 − 220.0)	0.063
Eicosapentaenoic aicd	44.0 (31.3 – 62.3)	41.1 (29.6 − 59.8)	62.8 (42.8 − 83.0)	0.034
Behenic acid	17.3 (14.0 – 21.5)	16.7 (13.4 − 21.0)	20.9 (15.6 − 25.3)	0.014
Docosatetraenoic acid	4.4 (3.5 – 5.7)	4.3 (3.4 − 5.7)	4.6 (3.8 − 6.8)	0.446
Docosapentaenoic acid	14.3 (11.2 – 19.5)	13.5 (10.7 − 18.2)	19.8 (15.4 − 26.1)	<0.001
Lignoceric acid	16.3 (12.9 – 20.4)	16.1 (12.5 − 19.4)	17.9 (14.5 − 22.6)	0.068

Supplementary Data

Docosahexaenoic acid	117.2 (87.7 – 145.8)	112.4 (82.0 − 138.5)	147.4 (112.2 − 172.3)	<0.001
Nervonic acid	42.9 (36.0 – 49.4)	42.8 (36.0 − 49.8)	44.4 (36.0 − 49.4)	0.888

Data are expressed as median (interquartile range). Data are expressed in μg/mL, except that total cholesterol, LDL-cholesterol, and HDL-cholesterol are in mg/dL.

HDL, high-density lipoprotein; LDL, low-density lipoprotein,

Supplementary Table 2. Difference in lipids according to the Eastern Cooperative Oncology Group performance status

Variables	ECOG-PS 0-1, n=140	ECOG-PS ≥2, n=8	*p*-value
LDL-cholesterol	88.0 (66.0 − 111.8)	71.5 (51.8 − 74.0)	0.032
HDL-cholesterol	39.5 (23.5 − 53.5)	44.0 (38.0 − 51.8)	0.138
Total cholesterol	183.5 (149.0 − 209.8)	147.5 (132.0 − 189.5)	0.078
Lauric acid	2.4 (1.4 − 4.2)	1.0 (0.8 − 1.1)	0.333
Myristic acid	22.8 (16.3 − 38.2)	12.6 (10.7 − 15.9)	0.021
Myristoleic acid	1.4 (0.9 − 2.7)	0.7 (0.4 − 1.1)	0.049
Palmitic acid	692.7 (570.0 − 843.6)	628.6 (503.8 − 721.8)	0.140
Palmitoleic acid	63.6 (46.0 − 82.8)	47.5 (36.3 − 76.3)	0.240
Stearic acid	216.2 (174.9 − 253.9)	176.9 (147.9 − 199.0)	0.038
Oleic acid	621.7 (502.4 − 795.8)	597.5 (489.5 − 723.4)	0.393
Linoleic acid	781.0 (623.2 − 969.8)	626.5 (574.9 − 702.6)	0.063
γ-linolenic acid	7.3 (4.9 − 10.9)	4.8 (3.7 − 6.6)	0.070
Linolenic acid	21.5 (15.1 − 33.8)	15.5 (11.5 − 18.1)	0.042
Arachidic acid	8.1 (6.4 − 9.8)	6.6 (5.9 − 9.1)	0.205
Eicosenoic acid	4.9 (3.9 − 6.6)	5.4 (3.5 − 6.5)	0.538
Eicosadienoic acid	6.7 (5.4 − 8.2)	5.1 (4.7 − 6.2)	0.068
Eicosatrienoic acid	2.3 (1.6 − 3.7)	1.6 (1.1 − 1.9)	0.077
Dihomo-γ-linolenic acid	35.5 (28.2 − 46.1)	23.3 (18.1 − 29.3)	0.013
Arachidonic acid	181.8 (149.2 − 208.6)	144.1 (132.8 − 192.6)	0.296
Eicosapentaenoic aicd	45.0 (31.1 − 62.3)	35.5 (31.5 − 88.2)	0.990
Behenic acid	17.3 (14.1 − 21.7)	13.3 (12.6 − 17.0)	0.025

Supplementary Data

Docosatetraenoic acid	4.4 (3.6 − 5.7)	3.5 (2.8 − 4.7)	0.102
Docosapentaenoic acid	14.3 (11.2 − 19.6)	13.0 (11.5 − 14.9)	0.276
Lignoceric acid	16.9 (13.3 − 20.5)	12.4 (10.2 − 13.8)	0.005
Docosahexaenoic acid	116.7 (84.2 − 146.3)	124.6 (99.7 − 135.1)	0.868
Nervonic acid	42.7 (35.9 − 47.9)	52.9 (46.7 − 58.2)	0.009

Data are expressed as median (interquartile range). Data are expressed in μg/mL, except that total cholesterol, LDL-cholesterol, and HDL-cholesterol are in mg/dL.

HDL, high-density lipoprotein; LDL, low-density lipoprotein,

Supplementary Table 3: Correlations between lipid levels and clinical factors

	BMI	TC	LDL-C	HDL-C	LauA	MA	MOA	PA	POA	SA	OA	LOA	GLA	LA
Age	-0.13	-0.12	-0.12	-0.05	-0.20	-0.21	-0.09	-0.22	-0.02	-0.31	-0.22	-0.24	-0.19	-0.13
BMI		0.10	0.16	-0.08	0.03	0.28	0.24	0.28	0.13	0.25	0.28	0.30	0.18	0.33
TC			0.86	0.38	0.17	0.51	0.43	0.68	0.41	0.67	0.57	0.79	0.37	0.50
LDL-C				0.25	0.19	0.48	0.40	0.54	0.30	0.56	0.43	0.70	0.36	0.49
HDL-C					0.05	0.11	0.06	0.14	-0.04	0.21	-0.02	0.28	0.25	0.09
LauA						0.61	0.31	0.34	0.04	0.43	0.28	0.26	0.19	0.21
MA							0.88	0.84	0.52	0.81	0.74	0.63	0.54	0.57
MOA								0.75	0.61	0.66	0.66	0.51	0.47	0.46
PA									0.76	0.92	0.94	0.79	0.62	0.64
POA										0.60	0.80	0.44	0.52	0.44
SA											0.86	0.82	0.57	0.65
OA												0.74	0.55	0.67
LOA													0.42	0.74
GLA														0.40
	AraA	**EEA**	**EDA**	**ETA**	**DGLA**	**AA**	**EPA**	**BA**	**DTA**	**DPA**	**LigA**	**DHA**	**NA**	
Age	-0.26	-0.19	-0.21	-0.11	-0.24	-0.12	0.18	-0.32	-0.22	-0.01	-0.27	0.04	0.11	
BMI	0.26	0.23	0.26	0.07	0.31	0.08	-0.04	0.21	0.14	0.11	0.13	0.12	-0.22	
TC	0.73	0.44	0.64	0.31	0.53	0.46	0.28	0.78	0.36	0.51	0.78	0.49	0.42	
LDL-C	0.61	0.31	0.55	0.27	0.50	0.43	0.34	0.68	0.35	0.54	0.68	0.48	0.25	
HDL-C	0.16	0.00	0.13	0.14	0.19	0.25	0.16	0.30	0.10	0.16	0.34	0.21	0.04	
LauA	0.34	0.22	0.13	0.19	0.20	0.16	0.01	0.34	0.21	0.12	0.33	0.08	-0.06	

Supplementary Data

MA	0.61	0.59	0.64	0.52	0.62	0.34	0.12	0.51	0.62	0.51	0.48	0.32	-0.07	
MOA	0.45	0.49	0.58	0.47	0.55	0.29	0.11	0.34	0.62	0.47	0.35	0.26	-0.03	
PA	0.74	0.72	0.82	0.58	0.73	0.49	0.10	0.62	0.74	0.59	0.55	0.41	0.17	
POA	0.34	0.55	0.66	0.59	0.61	0.40	0.07	0.20	0.76	0.53	0.20	0.31	0.16	
SA	0.80	0.70	0.79	0.51	0.69	0.51	0.18	0.70	0.66	0.59	0.63	0.45	0.16	
OA	0.67	0.81	0.84	0.58	0.69	0.44	-0.01	0.51	0.74	0.53	0.43	0.33	0.20	
LOA	0.82	0.63	0.83	0.31	0.62	0.42	0.07	0.80	0.48	0.45	0.76	0.41	0.27	
GLA	0.33	0.34	0.46	0.80	0.82	0.56	0.07	0.38	0.73	0.42	0.35	0.10	-0.15	
LA	0.55	0.63	0.74	0.25	0.49	0.26	0.16	0.48	0.40	0.49	0.44	0.33	0.07	
AraA		0.59	0.66	0.28	0.49	0.45	0.15	0.83	0.38	0.42	0.72	0.40	0.44	
EEA			0.77	0.39	0.48	0.30	0.02	0.39	0.52	0.37	0.31	0.30	0.23	
EDA				0.44	0.72	0.34	0.02	0.55	0.64	0.48	0.50	0.36	0.23	
ETA					0.74	0.54	-0.02	0.28	0.74	0.39	0.27	0.10	-0.02	
DGLA						0.53	-0.01	0.52	0.77	0.44	0.49	0.17	0.00	
AA							0.14	0.42	0.67	0.38	0.42	0.41	0.33	
EPA								0.11	-0.08	0.72	0.17	0.62	0.15	
BA									0.34	0.34	0.94	0.27	0.28	
DTA										0.43	0.31	0.18	0.01	
DPA											0.36	0.71	0.12	
LigA												0.30	0.26	
DHA													0.34	

Data are expressed as Pearson correlation coefficient.

Supplementary Data

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; LauA, lauric acid; MA, myristic acid; MOA, myristoleic acid; PA, palmitic acid; POA, palmitoleic acid; SA, stearic acid; OA, oleic acid, LOA, linoleic acid; GLA, γ-linolenic acid; LA, linolenic acid; AraA, arachidic acid; EEA, eicosenoic acid; EDA, eicosadienoic acid; ETA, eicosatrienoic acid; DGLA, dihomo-γ-linolenic acid; AA, arachidonic acid; EPA, eicosapentaenoic acid; BA, behenic acid; DTA, docosatetraenoic acid; DPA, docosapentaenoic acid; LigA, lignoceric acid; DHA, docosahexaenoic acid; NA, nervonic acid

Supplementary Table 4. Univariate Cox proportional hazard analyses of progression-free survival

Variables	Hazard ratio	*p*-value
Age, per 10-year increase	1.02 (0.84 − 1.23)	0.866
Sex, male	0.62 (0.40 − 0.99)	0.048
Body-mass index,	0.96 (0.90 − 1.02)	0.169
Smoking, ever-smoker	0.52 (0.32 − 0.92)	0.025
Use of statins	1.23 (0.72 − 1.97)	0.434
ECOG-PS,		
0 vs. 1	0.84 (0.58 − 1.21)	0.341
0 vs. ≥2	0.42 (0.21 − 0.96)	0.040
1 vs. ≥2	0.50 (0.25 − 1.15)	0.098
Pathology, squamous cell (vs. non-squamous)	1.36 (0.94 − 1.95)	0.105
Stage, IIIb (vs. IV/ recurrent)	0.85 (0.54 − 1.30)	0.471
PD-L1 expression (TPS),		
1 – 49% vs. <1%	0.86 (0.58 – 1.26)	0.444
≥50% vs. <1%	0.54 (0.29 – 0.93)	0.025
≥50% vs. 1 – 49%	0.63 (0.33 – 1.12)	0.117
Treatment line, 2nd (vs. ≥3rd)	1.55 (1.08 – 2.24)	0.017
LDL-cholesterol[a]	0.91 (0.86 – 0.97)	0.004
HDL-cholesterol[a]	0.83 (0.70 – 0.97)	0.019
Total cholesterol[a]	0.96 (0.92 – 1.00)	0.042
Lauric acid[b]	0.81 (0.62 – 0.97)	0.020
Myristic acid[b]	0.90 (0.81 – 0.98)	0.026
Myristoleic acid[c]	0.87 (0.76 – 0.98)	0.038
Palmitic acid[d]	0.94 (0.86 – 1.02)	0.165
Palmitoleic acid[b]	0.97 (0.92 – 1.03)	0.348
Stearic acid[d]	0.77 (0.57 – 1.01)	0.070

Oleic acid[d]	0.96 (0.89 – 1.03)	0.287
Linoleic acid[d]	0.92 (0.85 – 0.99)	0.048
γ-linolenic acid[c]	0.98 (0.95 – 1.01)	0.270
Linolenic acid[c]	0.99 (0.98 – 1.01)	0.435
Arachidic acid[c]	0.94 (0.87 – 1.01)	0.101
Eicosenoic acid[c]	0.93 (0.86 – 1.01)	0.093
Eicosadienoic acid[c]	0.92 (0.85 – 0.99)	0.040
Eicosatrienoic acid[c]	0.95 (0.86 – 1.03)	0.243
Dihomo-γ-linolenic acid[c]	0.99 (0.98 – 1.00)	0.071
Arachidonic acid[b]	0.99 (0.95 – 1.03)	0.531
Eicosapentaenoic aid[b]	1.00 (0.95 – 1.05)	0.945
Behenic acid[c]	0.97 (0.94 – 1.01)	0.103
Docosatetraenoic acid[c]	0.94 (0.85 – 1.03)	0.180
Docosapentaenoic acid[c]	0.99 (0.96 – 1.01)	0.356
Lignoceric acid[c]	0.97 (0.93 – 1.01)	0.116
Docosahexaenoic acid[b]	0.98 (0.94 – 1.02)	0.363
Nervonic acid[b]	1.00 (0.84 – 1.20)	0.981

ECOG-PS, Eastern Cooperative Oncology Group performance status; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

[a]per 10 mg/dL increase

[b]per 10 μg/mL increase

[c]per 1 μg/mL increase

[d]per 100 μg/mL increase

Supplementary Table 5. Multivariate Cox proportional hazard analyses of progression-free survival: Other combinations in the multiple-lipid analyses

Variables	Combination B		Combination C		Combination D	
	Hazard ratio	*p*-value	Hazard ratio	*p*-value	Hazard ratio	*p*-value
HDL-cholesterol[a]	0.84 (0.70 – 1.00)	0.057	0.85 (0.71 – 1.01)	0.061	0.84 (0.70 – 1.01)	0.058
Total cholesterol[a]	0.96 (0.89 – 1.03)	0.287				
Lauric acid[b]	0.81 (0.59 – 1.01)	0.058	0.84 (0.59 – 1.07)	0.187	0.88 (0.67 – 1.04)	0.156
Myristic acid[b]			1.02 (0.84 – 1.22)	0.851		
Myristoleic acid[c]	0.93 (0.77 – 1.10)	0.411			0.95 (0.79 – 1.11)	0.527
Stearic acid[d]	1.50 (0.76 – 2.92)	0.242				
Linoleic acid[d]			0.93 (0.82 – 1.07)	0.316	0.94 (0.82 – 1.07)	0.364
Eicosenoic acid[c]	0.97 (0.86 – 1.08)	0.565	1.01 (0.90 – 1.12)	0.866	1.02 (0.91 – 1.12)	0.742
Dihomo-γ-linolenic acid[c]	0.99 (0.97 – 1.01)	0.424	0.99 (0.98 – 1.01)	0.442	1.00 (0.98 – 1.01)	0.631

Hazard ratio was adjusted by sex, smoking status, ECOG-PS, PD-L1 expression, and treatment line (2nd vs. ≥3rd).

[a]per 10 mg/dL increase

[b]per 10 μg/mL increase

[c]per 1 μg/mL increase

[d]per 100 μg/mL increase

Supplementary Table 6. Univariate Cox proportional hazard analyses of overall survival

Variables	Hazard ratio	*p*-value
Age, per 10-year increase	1.01 (0.82 – 1.27)	0.898
Sex, male	0.85 (0.52 – 1.44)	0.522
Body-mass index, per 1kg/m^2 increase	0.88 (0.82 – 0.95)	<0.001
Smoking, ever-smoker	0.73 (0.42 – 1.38)	0.318
Use of statins	1.00 (0.52 – 1.77)	0.991
ECOG-PS,		
0 vs. 1	0.63 (0.42 – 0.97)	0.035
0 vs. ≥2	0.28 (0.13 – 0.75)	0.014
1 vs. ≥2	0.44 (0.20 – 1.17)	0.095
Pathology, squamous cell (vs. non-squamous)	1.74 (1.14 – 2.63)	0.010
Stage, IIIb (vs. IV/ recurrent)	0.80 (0.47 – 1.29)	0.370
PD-L1 expression (TPS),		
1 – 49% vs. <1%	1.00 (0.64 – 1.55)	0.987
≥50% vs. <1%	0.49 (0.22 – 0.98)	0.045
≥50% vs. 1 – 49%	0.49 (0.21 – 1.02)	0.055
Treatment line, 2nd (vs. ≥3rd)	1.21 (0.81 – 1.83)	0.350
LDL-cholesterol[a]	0.88 (0.82 − 0.95)	<0.001
HDL-cholesterol[a]	0.79 (0.65 − 0.95)	0.015
Total cholesterol[a]	0.94 (0.90 − 0.98)	0.011
Lauric acid[b]	0.85 (0.61 – 1.03)	0.200
Myristic acid[b]	0.88 (0.78 – 0.98)	0.025
Myristoleic acid[c]	0.86 (0.73 – 0.98)	0.043
Palmitic acid[d]	0.93 (0.85 – 1.01)	0.115
Palmitoleic acid[b]	0.97 (0.92 – 1.03)	0.354
Stearic acid[d]	0.71 (0.51 – 0.98)	0.042

Supplementary Data

Oleic acid[d]	0.96 (0.88 – 1.03)	0.259
Linoleic acid[d]	0.87 (0.80 – 0.95)	0.003
γ-linolenic acid[c]	0.98 (0.95 – 1.01)	0.250
Linolenic acid[c]	0.99 (0.98 – 1.00)	0.232
Arachidic acid[c]	0.93 (0.86 – 1.01)	0.100
Eicosenoic acid[c]	0.93 (0.84 – 1.01)	0.112
Eicosadienoic acid[c]	0.89 (0.81 – 0.97)	0.016
Eicosatrienoic acid[c]	0.94 (0.84 – 1.03)	0.220
Dihomo-γ-linolenic acid[c]	0.99 (0.97 – 1.00)	0.056
Arachidonic acid[b]	0.97 (0.92 – 1.01)	0.181
Eicosapentaenoic aid[b]	1.02 (0.96 – 1.09)	0.465
Behenic acid[c]	0.95 (0.91 – 0.99)	0.017
Docosatetraenoic acid[c]	0.92 (0.83 – 1.02)	0.128
Docosapentaenoic acid[c]	1.00 (0.97 – 1.03)	0.999
Lignoceric acid[c]	0.94 (0.90 – 0.98)	0.006
Docosahexaenoic acid[b]	0.98 (0.93 – 1.03)	0.384
Nervonic acid[b]	1.17 (0.96 – 1.44)	0.120

ECOG-PS, Eastern Cooperative Oncology Group performance status; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

[a]per 10 mg/dL increase

[b]per 10 μg/mL increase

[c]per 1 μg/mL increase

[d]per 100 μg/mL increase

Supplementary Table 7. Multivariate Cox proportional hazard analyses of overall survival: Other combinations in the multiple-lipid analyses

Variables	Combination B		Combination C		Combination D		Combination E	
	Hazard ratio	*p*-value	Hazard ratio	*p*-value	Hazard ratio	*p*-value	Hazard ratio	*p*-value
LDL-cholesterol[a]	0.85 (0.76 – 0.95)	0.003	0.88 (0.78 – 0.98)	0.017	0.88 (0.78 – 0.98)	0.018	0.86 (0.77 – 0.96)	0.008
HDL-cholesterol[a]	0.81 (0.65 – 0.98)	0.030	0.81 (0.65 – 0.99)	0.040	0.81 (0.65 – 0.99)	0.039	0.80 (0.65 – 0.98)	0.034
Myristic acid[b]			1.02 (0.88 – 1.18)	0.784			1.01 (0.87 – 1.16)	0.861
Myristoleic acid[c]	0.92 (0.74 – 1.10)	0.374			1.01 (0.85 – 1.17)	0.935		
Stearic acid[d]	1.61 (0.83 – 3.04)	0.158						
Eicosadienoic acid[c]			0.99 (0.88 – 1.12)	0.957	1.00 (0.88 – 1.12)	0.981	0.99 (0.87 – 1.11)	0.870
Dihomo-γ-linolenic acid[c]	1.00 (0.98 – 1.02)	0.837						
Behenic acid[c]	1.00 (0.98 – 1.02)	0.997					1.03 (0.96 – 1.09)	0.382
Lignoceric acid[c]			1.01 (0.95 – 1.08)	0.722	1.01 (0.95 – 1.07)	0.681		
	Combination F		**Combination G**		**Combination H**		**Combination I**	
LDL-cholesterol[a]	0.87 (0.78 – 0.96)	0.008						
HDL-cholesterol[a]	0.80 (0.65 – 0.98)	0.033	0.80 (0.64 – 0.99)	0.039	0.78 (0.62 – 0.97)	0.026	0.78 (0.62 – 0.97)	0.026
Total cholesterol[a]			0.95 (0.88 – 1.03)	0.188	0.99 (0.92 – 1.06)	0.704	0.99 (0.92 – 1.06)	0.693
Myristic acid[b]					0.99 (0.85 – 1.13)	0.877		

Supplementary Data

Myristoleic acid[c]	1.01 (0.85 – 1.17)	0.915	0.92 (0.74 – 1.09)	0.365			0.98 (0.82 – 1.15)	0.853
Stearic acid[d]			1.42 (0.75 – 2.58)	0.274				
Eicosadienoic acid[c]	0.99 (0.87 – 1.11)	0.889			0.95 (0.83 – 1.07)	0.439	0.95 (0.84 – 1.07)	0.437
Dihomo-γ-linolenic acid[c]			1.00 (0.98 – 1.02)	0.861				
Behenic acid[c]	1.03 (0.97 – 1.09)	0.355						

Hazard ratio was adjusted by clinical factors including sex, body-mass index, ECOG-PS, pathology, and PD-L1 expression. Total cholesterol, myristoleic acid, linoleic acid, and lignoceric acid were excluded for multiple lipids analysis in Table 3, because there were strong correlations between LDL-cholesterol and total cholesterol (r=0.86), myristic acid and myristoleic acid (r=0.88), myristic acid and stearic acid (r=0.81), linoleic acid and steric acid (r=0.82), linoleic acid and eicosadienoic acid (r=0.83), linoleic acid and behenic acid (r=0.80), and lignoceric acid and behenic acid (r=0.94). Combination A employed total cholesterol (instead of LDL-cholesterol), Combination B employed myristic acid, linoleic acid, and lignoceric acid (instead of myristoleic acid, stearic acid, eicosadienoic acid and behenic acid), and Combination C employed total cholesterol, myristic acid, linoleic acid, and lignoceric acid (instead of LDL-cholesterol, myristoleic acid, stearic acid, eicosadienoic acid and behenic acid).

[a]per 10 mg/dL increase

[b]per 10 μg/mL increase

[c]per 1 μg/mL increase

[d]per 100 μg/mL increase

Supplementary Table 8. Univariate logistic regression analyses of objective response

Variables	Odds ratio	*p*-value
Age, per 10-year increase	0.83 (0.55 − 1.27)	0.381
Sex, male	8.89 (1.77 − 1.62×10^2)	0.004
Body-mass index, per 1kg/m^2 increase	1.07 (0.95 − 1.22)	0.267
Smoking, ever-smoker	9.96×10^6 (2.71 −N.E.)	0.002
Use of statins	0.85 (0.23 − 2.55)	0.789
ECOG-PS,		
0 vs. 1	1.10 (0.50 − 2.46)	0.805
0 vs. ≥2	3.51×10^6 (1.12 − N.E.)	0.040
1 vs. ≥2	3.17×10^6 (0.99 − N.E.)	0.051
Pathology, squamous cell (vs. non-squamous)	0.81 (0.35 − 1.80)	0.604
Stage, IIIb (vs. IV/ recurrent)	1.15 (0.44 − 2.79)	0.762
PD-L1 expression (TPS),		
1 – 49% vs. <1%	2.34 (0.91 − 6.24)	0.078
≥50% vs. <1%	7.94 (2.68 − 24.88)	<0.001
≥50% vs. 1 – 49%	3.39 (1.17 − 10.20)	0.025
Treatment line, 2nd (vs. ≥3rd)	0.70 (0.32 − 1.52)	0.365
LDL-cholesterol[a]	1.11 (0.97 − 1.25)	0.121
HDL-cholesterol[a]	1.10 (0.82 − 1.48)	0.535
Total cholesterol[a]	1.05 (0.96 − 1.15)	0.258
Lauric acid[b]	1.15 (0.87 − 1.52)	0.281
Myristic acid[b]	1.03 (0.85 − 1.23)	0.711
Myristoleic acid[c]	1.00 (0.79 − 1.23)	0.984
Palmitic acid[d]	1.05 (0.89 − 1.23)	0.562

Palmitoleic acid[b]	1.02 (0.93 − 1.11)	0.628
Stearic acid[d]	1.25 (0.70 − 2.16)	0.436
Oleic acid[d]	1.02 (0.88 − 1.17)	0.783
Linoleic acid[d]	1.07 (0.91 − 1.26)	0.415
γ-linolenic acid[c]	1.01 (0.95 − 1.07)	0.689
Linolenic acid[c]	0.99 (0.96 − 1.02)	0.539
Arachidic acid[c]	1.12 (0.96 − 1.30)	0.159
Eicosenoic acid[c]	1.00 (0.84 − 1.17)	0.998
Eicosadienoic acid[c]	1.10 (0.95 − 1.27)	0.185
Eicosatrienoic acid[c]	1.05 (0.88 − 1.24)	0.541
Dihomo-γ-linolenic acid[c]	1.02 (0.99 − 1.04)	0.201
Arachidonic acid[b]	0.99 (0.91 − 1.07)	0.845
Eicosapentaenoic aid[b]	0.99 (0.86 − 1.11)	0.826
Behenic acid[c]	1.05 (0.98 − 1.13)	0.157
Docosatetraenoic acid[c]	1.04 (0.88 − 1.21)	0.638
Docosapentaenoic acid[c]	1.01 (0.95 − 1.06)	0.764
Lignoceric acid[c]	1.04 (0.96 − 1.12)	0.332
Docosahexaenoic acid[b]	0.95 (0.86 − 1.05)	0.318
Nervonic acid[b]	1.01 (0.70 − 1.45)	0.957

Data are expressed as odds ratio (95% confident interval). N.E., not estimable

ECOG-PS, Eastern Cooperative Oncology Group performance status; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

[a]per 10 mg/dL increase

[b]per 10 μg/mL increase

[c]per 1 μg/mL increase

[d]per 100 μg/mL increase

Supplementary Table 9. Characteristics of the patients who received cytotoxic chemotherapy

	n=113
Age, years	66 (61 − 72)
Sex, men	84 (74.3)
Smoking status, ever-smoker	88 (77.9)
Body-mass index, kg/m^2	21.9 (19.0 − 23.9)
Use of statins	12 (10.6)
ECOG-PS, 0 / 1 / ≥2	69 (61.1) / 36 (31.9) / 8 (7.1)
Stage, IIIb / IV / recurrence	16 (14.2) / 97 (85.8) / 0 (0)
Pathology, adeno / squamous / others	65 (57.5) / 31 (27.4) / 17 (15.0)
PD-L1 expression: TPS, <1% / ≥1 − 49% / ≥50% / unknown	6 (5.3)8.5 / 3 (2.7) / 4 (3.5) / 100 (88.5)
***EGFR* mutation, positive / wild / unknown**	14 (12.4) / 98 (86.7) / 1 (0.9)
***ALK* fusion gene, positive / wild / unknown**	1 (0.9) / 73 (64.6) / 39 (34.5)
Treatment line, 1st / 2nd / ≥ 3rd	113 (100) / 0 (0) / 0 (0)

Data are expressed as median (interquartile range) or number (%).

ALK, anaplastic lymphoma kinase; CR, complete response; ECOG-PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PD, progressive disease; PR, partial response; SD, stable disease.

Supplementary Table 10. Univariate and multivariate Cox proportional hazard analyses of progression-free survival in the chemotherapy cohort

Variables	Univariate		Multivariate (single lipid analysis)	
	Hazard ratio	*p*-value	Hazard ratio[e]	*p*-value
Age, per 10-year increase	1.35 (1.06 − 1.74)	0.020		
Sex, male	1.06 (0.66 − 1.78)	0.823		
Body-mass index, per 1kg/m^2 increase	0.98 (0.92 − 1.05)	0.596		
Smoking, ever-smoker	1.32 (0.81 − 2.28)	0.273		
Use of statins	1.11 (0.53 − 2.06)	0.767		
ECOG-PS,				
0 vs. 1	0.66 (0.41 − 1.07)	0.089		
0 vs. ≥2	0.28 (0.11 − 0.96)	0.044		
1 vs. ≥2	0.43 (0.16 − 1.47)	0.160		
Pathology, squamous cell (vs. non-squamous)	1.14 (0.70 − 1.82)	0.587		
Stage, IIIb (vs. IV/ recurrent)	0.85 (0.39 − 1.61)	0.633		
Treatment,				
cisplatin vs. carboplatin	0.49 (0.24 − 0.89)	0.017		
PEM-base vs. non-PEM / non-TAX	0.57 (0.30 − 1.17)	0.119		
TAX-base vs. non-PEM / non-TAX	0.73 (0.37 − 1.54)	0.392		
TAX-base vs. PEM-base	1.29 (0.79 − 2.06)	0.300		
LDL-cholesterol[a]	0.97 (0.90 − 1.04)	0.445	0.99 (0.92 − 1.08)	0.891
HDL-cholesterol[a]	0.95 (0.90 − 1.00)	0.054	0.93 (0.76 − 1.13)	0.496
Total cholesterol[a]	0.95 (0.90 − 0.99)	0.044	0.97 (0.92 − 1.03)	0.368
Lauric acid[b]	1.13 (0.64 − 1.73)	0.666	1.17 (0.65 − 1.80)	0.548
Myristic acid[b]	0.97 (0.86 − 1.06)	0.513	0.98 (0.87 − 1.08)	0.736
Myristoleic acid[c]	0.96 (0.84 − 1.08)	0.555	0.97 (0.84 − 1.09)	0.683
Palmitic acid[d]	0.98 (0.89 − 1.06)	0.690	1.00 (0.91 − 1.08)	0.991
Palmitoleic acid[b]	1.00 (0.95 − 1.04)	0.870	0.99 (0.94 − 1.04)	0.651

Supplementary Data

Stearic acid[d]	0.89 (0.59 − 1.27)	0.536	1.04 (0.70 − 1.49)	0.821
Oleic acid[d]	0.99 (0.90 − 1.08)	0.864	1.01 (0.91 − 1.10)	0.873
Linoleic acid[d]	0.88 (0.79 − 0.98)	0.018	0.93 (0.83 − 1.03)	0.190
γ-linolenic acid[c]	0.97 (0.91 − 1.02)	0.244	1.00 (0.94 − 1.04)	0.897
Linolenic acid[c]	0.98 (0.96 − 1.00)	0.080	0.99 (0.97 − 1.00)	0.175
Arachidic acid[c]	1.00 (0.90 − 1.10)	0.959	1.05 (0.94 − 1.16)	0.381
Eicosenoic acid[c]	0.96 (0.85 − 1.07)	0.530	0.98 (0.85 − 1.09)	0.687
Eicosadienoic acid[c]	0.86 (0.74 − 0.98)	0.037	0.88 (0.76 − 1.01)	0.075
Eicosatrienoic acid[c]	1.01 (0.87 − 1.14)	0.846	1.04 (0.90 − 1.17)	0.546
Dihomo-γ-linolenic acid[c]	0.98 (0.96 − 1.00)	0.053	0.99 (0.97 − 1.01)	0.335
Arachidonic acid[b]	0.96 (0.91 − 1.00)	0.046	0.97 (0.93 − 1.02)	0.285
Eicosapentaenoic aid[b]	1.00 (0.92 − 1.06)	0.891	1.01 (0.94 − 1.08)	0.689
Behenic acid[c]	0.97 (0.93 − 1.01)	0.166	1.01 (0.96 − 1.06)	0.809
Docosatetraenoic acid[c]	0.80 (0.68 − 0.95)	0.010	0.85 (0.71 − 1.01)	0.073
Docosapentaenoic acid[c]	0.97 (0.94 − 1.01)	0.132	0.98 (0.95 − 1.02)	0.388
Lignoceric acid[c]	0.96 (0.91 − 0.99)	0.056	0.99 (0.94 − 1.04)	0.719
Docosahexaenoic acid[b]	0.96 (0.92 − 1.01)	0.142	0.98 (0.93 − 1.02)	0.341
Nervonic acid[b]	1.18 (0.93 − 1.47)	0.151	1.13 (0.88 − 1.43)	0.330

ECOG-PS, Eastern Cooperative Oncology Group performance status; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PEM, pemetrexed; TAX, taxane.

[a]per 10 mg/dL increase

[b]per 10 μg/mL increase

[c]per 1 μg/mL increase

[d]per 100 μg/mL increase

[e]Adjusted by age, sex, ECOG-PS, and cisplatin-based therapy (vs. carboplatin-based therapy).

Supplementary Table 11. Univariate Cox proportional hazard analyses of overall survival in the chemotherapy cohort

Variables	Hazard ratio	*p*-value
Age, per 10-year increase	1.44 (1.11 − 1.88)	0.005
Sex, male	1.14 (0.69 − 1.95)	0.624
Body-mass index, per 1kg/m^2 increase	0.95 (0.89 − 1.03)	0.226
Smoking, ever-smoker	2.29 (1.29 − 4.40)	0.004
Use of statins	1.19 (0.53 − 2.36)	0.647
ECOG-PS,		
0 vs. 1	0.63 (0.38 − 1.06)	0.079
0 vs. ≥2	0.06 (0.02 − 0.19)	<0.001
1 vs. ≥2	0.09 (0.03 − 0.30)	<0.001
Pathology, squamous cell (vs. non-squamous)	1.20 (0.70 − 1.99)	0.502
Stage, IIIb (vs. IV/ recurrent)	1.19 (0.57 − 2.23)	0.621
Treatment,		
cisplatin vs. carboplatin	0.73 (0.38 − 1.29)	0.292
PEM-base vs. non-PEM / non-TAX	0.63 (0.31 − 1.40)	0.237
TAX-base vs. non-PEM / non-TAX	0.75 (0.36 − 1.71)	0.479
TAX-base vs. PEM-base	1.20 (0.72 − 1.97)	0.472
LDL-cholesterol[a]	0.93 (0.86 − 1.01)	0.077
HDL-cholesterol[a]	1.05 (0.87 − 1.24)	0.629
Total cholesterol[a]	0.97 (0.92 − 1.02)	0.240
Lauric acid[b]	0.97 (0.89 − 1.04)	0.391
Myristic acid[b]	0.89 (0.75 − 1.02)	0.093
Myristoleic acid[c]	0.89 (0.74 − 1.04)	0.167
Palmitic acid[d]	0.94 (0.83 − 1.05)	0.295
Palmitoleic acid[b]	0.98 (0.92 − 1.04)	0.536
Stearic acid[d]	0.75 (0.45 − 1.17)	0.214

Oleic acid[d]	0.96 (0.85 − 1.07)	0.498
Linoleic acid[d]	0.95 (0.85 − 1.06)	0.396
γ-linolenic acid[c]	1.00 (0.94 − 1.04)	0.914
Linolenic acid[c]	0.99 (0.97 − 1.01)	0.388
Arachidic acid[c]	0.98 (0.87 − 1.09)	0.739
Eicosenoic acid[c]	0.98 (0.85 − 1.11)	0.780
Eicosadienoic acid[c]	0.94 (0.81 − 1.08)	0.409
Eicosatrienoic acid[c]	1.05 (0.89 − 1.20)	0.509
Dihomo-γ-linolenic acid[c]	1.00 (0.98 − 1.02)	0.986
Arachidonic acid[b]	1.02 (0.97 − 1.07)	0.397
Eicosapentaenoic aid[b]	1.03 (0.95 − 1.10)	0.437
Behenic acid[c]	0.97 (0.92 − 1.02)	0.207
Docosatetraenoic acid[c]	1.02 (0.86 − 1.20)	0.852
Docosapentaenoic acid[c]	0.99 (0.96 − 1.03)	0.768
Lignoceric acid[c]	0.96 (0.92 − 1.01)	0.113
Docosahexaenoic acid[b]	1.00 (0.95 − 1.05)	0.873
Nervonic acid[b]	1.26 (0.99 − 1.60)	0.064

ECOG-PS, Eastern Cooperative Oncology Group performance status; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PEM, pemetrexed; TAX, taxane.

[a]per 10 mg/dL increase

[b]per 10 μg/mL increase

[c]per 1 μg/mL increase

[d]per 100 μg/mL increase

Supplementary Table 12. Univariate logistic regression analyses of objective response in the chemotherapy cohort

Variables	Odds ratio	*p*-value
Age, per 10-year increase	0.68 (0.45 − 1.02)	0.056
Sex, male	1.08 (0.46 − 2.53)	0.854
Body-mass index, per 1kg/m^2 increase	1.02 (0.91 − 1.14)	0.743
Smoking, ever-smoker	1.27 (0.52 − 3.10)	0.596
Use of statins	0.74 (0.22 − 2.46)	0.625
ECOG-PS,		
0 vs. 1	1.24 (0.55 − 2.81)	0.599
0 vs. ≥2	4.67 (0.88 − 24.83)	0.071
1 vs. ≥2	3.75 (0.66 − 21.15)	0.134
Pathology, squamous cell (vs. non-squamous)	0.76 (0.33 − 1.73)	0.508
Stage, IIIb (vs. IV/ recurrent)	0.55 (0.19 − 1.59)	0.266
Treatment,		
cisplatin vs. carboplatin	0.92 (0.35 − 2.44)	0.871
PEM-base vs. non-PEM / non-TAX	0.96 (0.30 − 3.04)	0.945
TAX-base vs. non-PEM / non-TAX	0.70 (0.21 − 2.38)	0.572
TAX-base vs. PEM-base	0.73 (0.32 − 1.67)	0.459
LDL-cholesterol[a]	1.08 (0.96 − 1.22)	0.203
HDL-cholesterol[a]	0.91 (0.69 − 1.20)	0.523
Total cholesterol[a]	1.02 (0.94 − 1.10)	0.646
Lauric acid[b]	1.01 (0.92 − 1.10)	0.839
Myristic acid[b]	1.04 (0.89 − 1.23)	0.611
Myristoleic acid[c]	1.06 (0.87 − 1.29)	0.584
Palmitic acid[d]	1.01 (0.89 − 1.15)	0.864
Palmitoleic acid[b]	1.01 (0.94 − 1.09)	0.738
Stearic acid[d]	0.80 (0.44 − 1.44)	0.447

Oleic acid[d]	0.98 (0.85 − 1.12)	0.740
Linoleic acid[d]	0.96 (0.82 − 1.13)	0.652
γ-linolenic acid[c]	0.99 (0.94 − 1.04)	0.647
Linolenic acid[c]	1.00 (0.97 − 1.04)	0.923
Arachidic acid[c]	1.03 (0.87 − 1.22)	0.764
Eicosenoic acid[c]	0.95 (0.78 − 1.15)	0.585
Eicosadienoic acid[c]	0.93 (0.75 − 1.16)	0.517
Eicosatrienoic acid[c]	0.89 (0.73 − 1.09)	0.243
Dihomo-γ-linolenic acid[c]	0.98 (0.96 − 1.01)	0.280
Arachidonic acid[b]	0.95 (0.88 − 1.01)	0.108
Eicosapentaenoic aid[b]	0.95 (0.84 − 1.08)	0.451
Behenic acid[c]	1.03 (0.96 − 1.11)	0.405
Docosatetraenoic acid[c]	0.80 (0.63 − 1.04)	0.087
Docosapentaenoic acid[c]	0.98 (0.92 − 1.03)	0.416
Lignoceric acid[c]	1.02 (0.95 − 1.10)	0.580
Docosahexaenoic acid[b]	0.97 (0.89 − 1.05)	0.429
Nervonic acid[b]	0.77 (0.49 − 1.19)	0.230

[a]per 10 mg/dL increase

[b]per 10 μg/mL increase

[c]per 1 μg/mL increase

[d]per 100 μg/mL increase