SUPPLEMENTAL TABLES

Supplemental Table 1. Extracellular forms of PD-L1 and outcomes in multiple malignancies.

	High sPD-L1 prognosis	PD-L1 protein-to-mRNA prognosis[1]	First Line IO	Non-First Line IO
Adrenocortical		↑		
Bladder		↑	Cisplatin-ineligible CPS10: P^2A^3	P^2 N^4
Breast	Poor[5]	↑	TNBC unresectable PD-L1>1%: A^3	
Biliary	Poor [6]			
Cervical		↗		P^2
Colon			MSI-high: P^2	
Gastric	Mainly poor[7–11] Poor in IO[12] Poor with EVs[13]	↓		P^2
Glioma (low-grade)		↑		
Head/Neck SCC		↗	P^2	N^4
Hepatocellular	Poor DFS and OS[14–18] or equivocal[19]	↑		P^2 N^4
Lung	Poor[20–23] Poor response in IO[12,24,25]		Metastatic NSCLC no muts: P^2A^3 SCLC: A^3	P^2 N^4
Lymphoma	BCL poor OS[26] poor response[27] decrease on tx positive[28] HL poor PFS[29] PTCL poor OS/PFS/response[30,31] NK/T poor OS/PFS[32,33]	↗		HL: P^2 N^4
Melanoma	Poor[34] Poor in IO[35]	↗	Unresectable/metastatic: P^2N^4 Adjuvant if LNs after resection: P^2	
Mesothelioma		↑		
Myeloma	Poor PFS[36,37]			
Ovarian (epithelial)	Poor OS and PFS in cisplatin-resp[38]			
Pancreatic	Decrease on tx positive[39]			
Prostate		↗		
Rectal	Poor DFS[40]			
Renal		↗	Advanced with axitinib: P^2	N^4
Sarcoma		↑		

Supplemental Table 1. Extracellular PD-L1 and survival. Cancers for which serum sPD-L1 and/or PD-L1 protein-to-mRNA ratios affect(s) prognosis in a previous study of Cancer Genome

Atlas (TCGA) data (increased improves survival)[1] and/or in which first-line or common second-line PD-(L)1 inhibitor therapy is FDA approved as a partial list. OS: overall survival. PFS: progression-free survival. IO: immunotherapy. A: atezolizumab. N: nivolumab. P: pembrolizumab. References:

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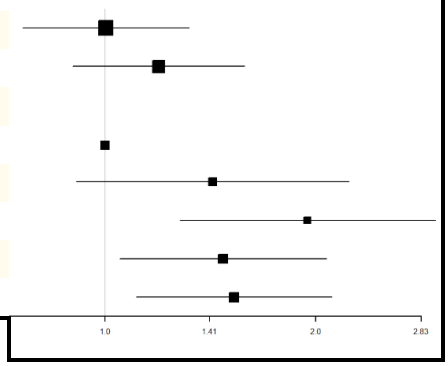
Supplemental Table 2. Baseline patient characteristics in the melanoma cohort.

	High sPD-L1 (n=216)	Low sPD-L1 (n=61)	Statistic
Age, years	60 (50, 69)	58 (50, 70)	F=0.10, P = 0.756[1]
Sex: M	137/216 (63)	31/60 (52)	X^2 = 2.73, P=0.10[2]
Stage			X^2 = 3. 95, P=0.139[2]
M1a	31/214 (14.5)	14/59 (23.7)	
M1b	54/214 (25.2)	17/59 (28.8)	
M1c	129/214 (60.3)	28/59 (47.5)	
sPD-L1, ng/uL	0.589 (0.370, 3.153)	0.216 (0.173, 0.249)	F=272.68 P < 0.001[1]
LDH, U/L	209 (168, 395)	187 (163, 298)	F=2.05 P = 0.154[1]

Supplemental Table 2. Baseline patient characteristics in the melanoma cohort. Patients with melanoma from three studies with retrospective data are compared by starting sPD-L1 level above or below the discovered survival cutoff (0.277ng/mL). Characteristics collected at entry into the study included age in years, sex, stage, sPD-L1, and LDH (lactate dehydrogenase). [1]Kruskal-Wallis. [2]Pearson.

Supplemental Table 3. Multivariate analysis in melanoma survival at diagnosis.

	Hazard Ratio	P value	
Age > 60 years	1.00 (0.76-1.32)	0.93	
Sex: M	1.19 (0.90-1.58)	0.25	
Stage			
M1a	1		
M1b	1.42 (0.91-2.23)	0.11	
M1c	1.94 (1.28-2.96)	0.002	**
sPD-L1 > 277ng/mL	1.47 (1.05-2.07)	0.025	*
LDH > 180U/L	1.53 (1.53, 2.11)	0.010	**



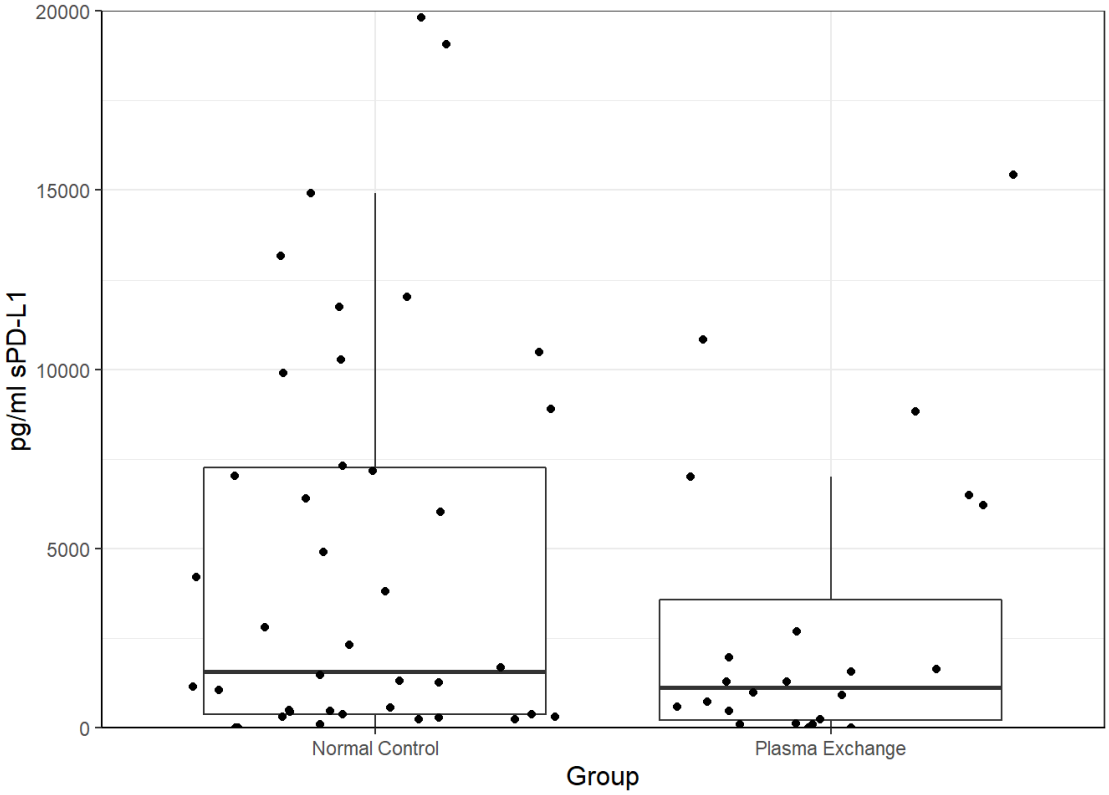
Supplemental Table 3. Multivariate analysis in melanoma survival at diagnosis. Cox proportional Hazards multivariate analysis was performed.

Supplemental Table 4. Reduction in EVs by subtype per exchange.	
% Reduction in total EVs per exchange	**(n=55)**
Mean (SD)	33.5 (89.4)
Median [Min, Max]	60.9 [-468, 99.1]
% Reduction PD-L1-positive EVs per exchange	**(n=13)**
Mean (SD)	73.1 (14.6)
Median [Min, Max]	72.3 [50.0, 98.5]
% Reduction in ADAM10-positive EVs per exchange	**(n=55)**
Mean (SD)	5.91 (126)
Median [Min, Max]	42.4 [-709, 99.5]

Supplemental Table 4. Reduction in EVs by subtype per exchange. Percent reduction in EVs for TPE sessions in which over one million pre-TPE EVs were present (*i.e.* above background noise levels) and no FFP was given.

SUPPLEMENTAL FIGURES

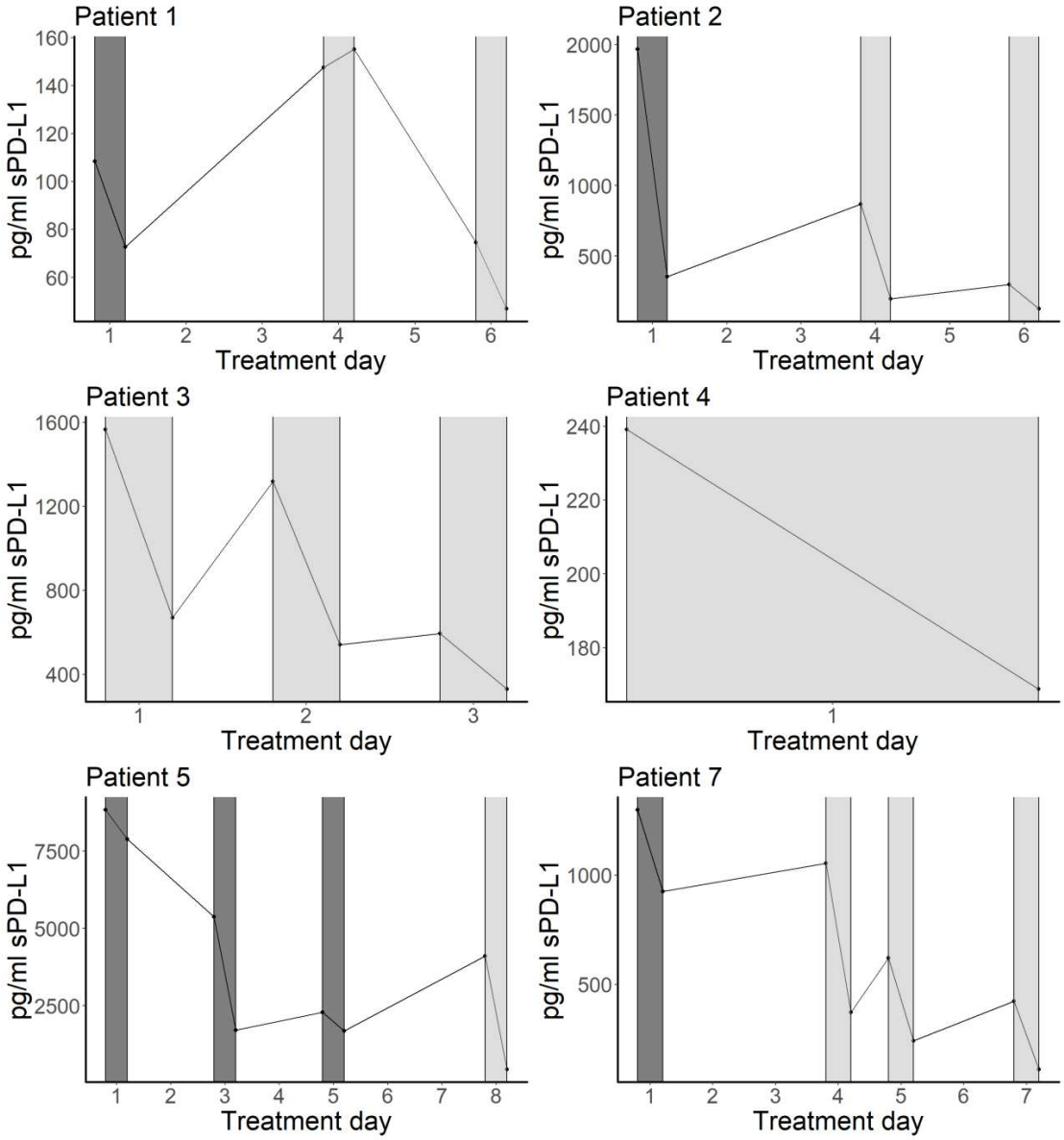
Supplemental Figure 1. Baseline plasma sPD-L1 in normal controls versus patients undergoing TPE.

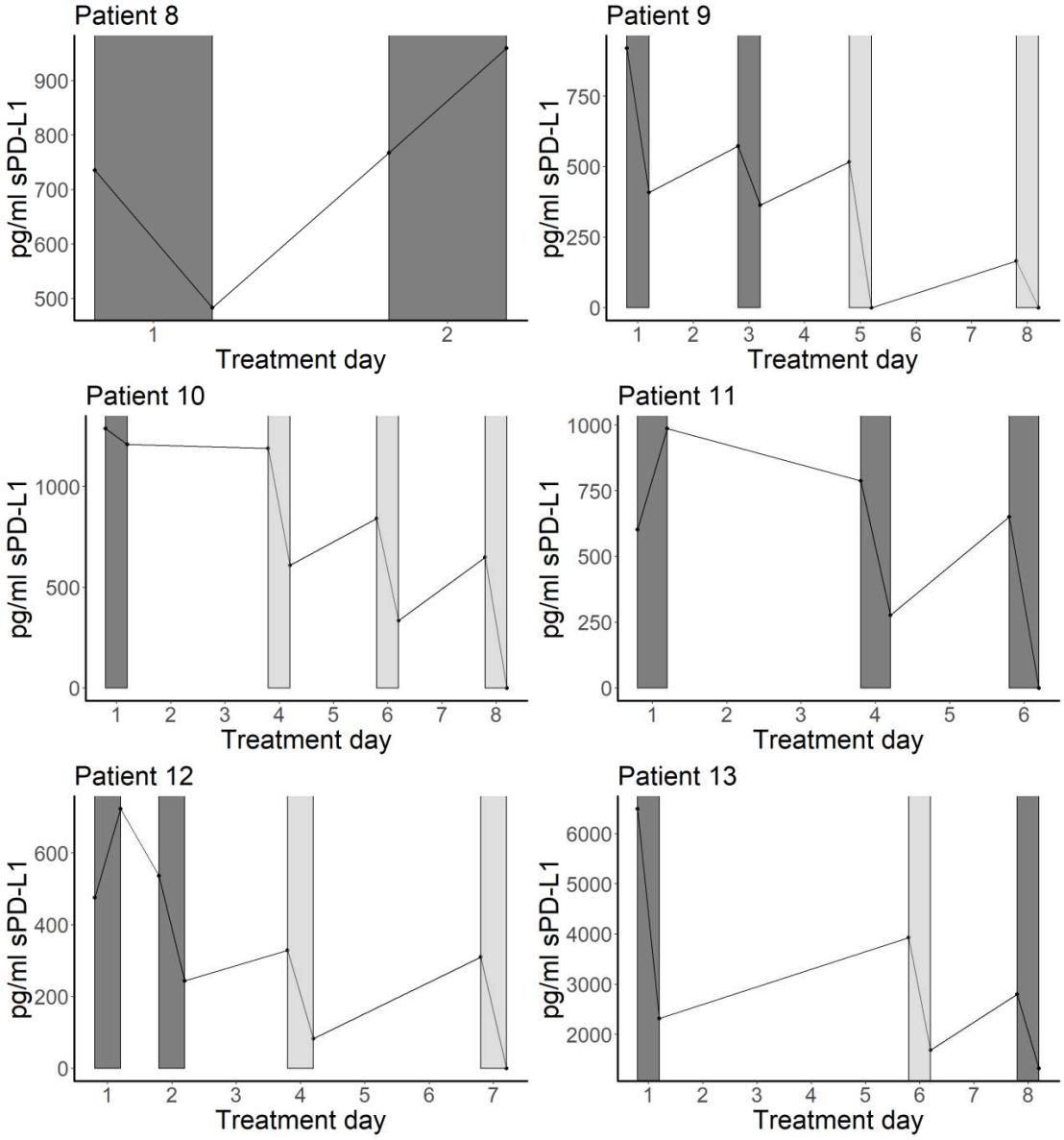


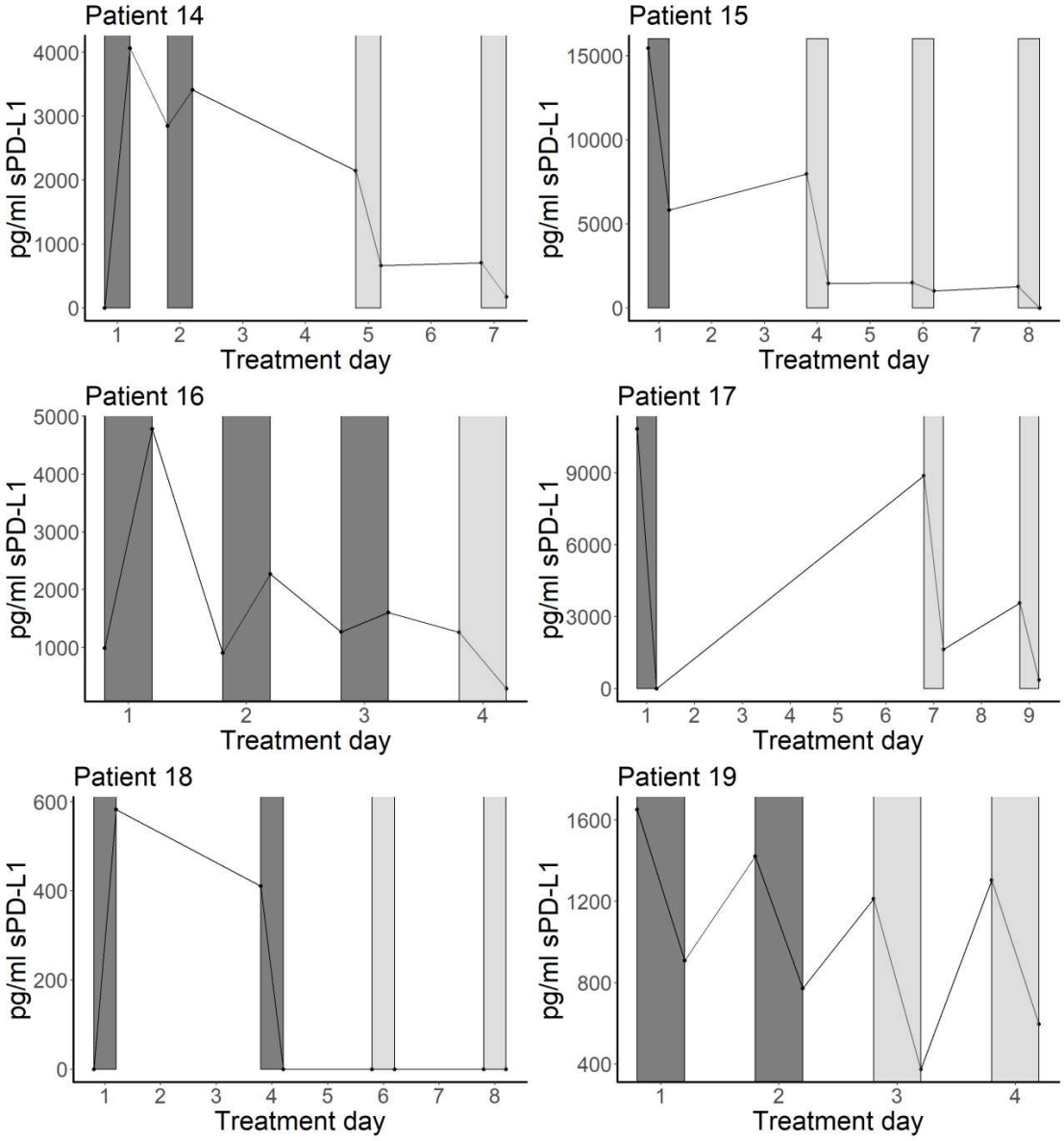
Baseline plasma sPD-L1 in normal controls versus patients undergoing TPE.					
	P value	mean	median	lower95CI	upper95CI
Normal Control	1	8188.0	2002.0	3167.9	13208.1
Plasma Exchange	0.1044	2898.8	1135.5	1554.4	4243.2

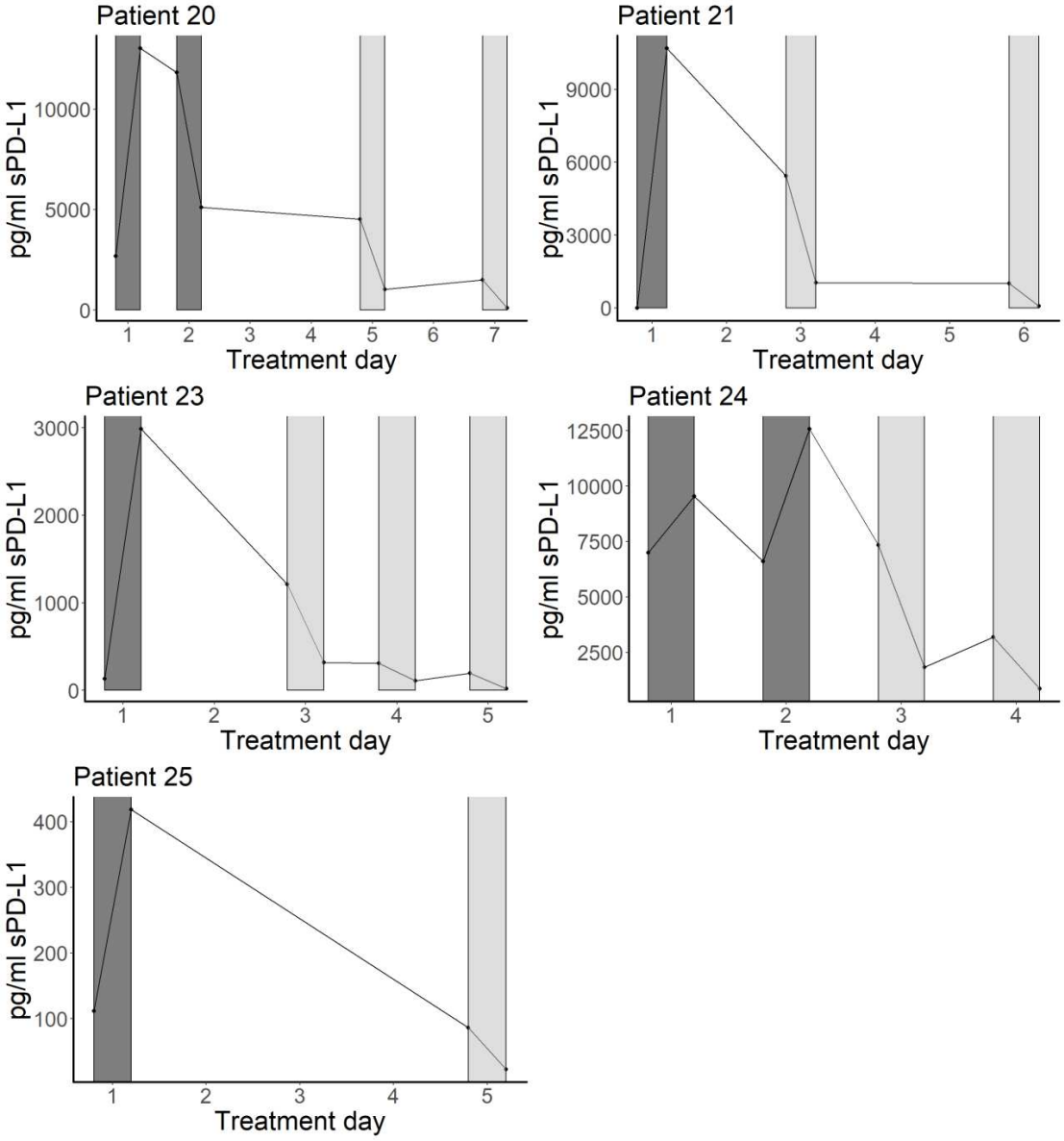
Supplemental Figure 1. Baseline plasma sPD-L1 in normal controls versus patients undergoing TPE. Levels of PD-L1 in patients undergoing TPE were not significantly lower than those of matched normal controls. Statistical table including p value (two-sided Student's *t* test), mean, and 95% confidence intervals are shown.

Supplemental Figure 2. Plasma sPD-L1 in all TPE treatment courses (including sessions involving FFP).



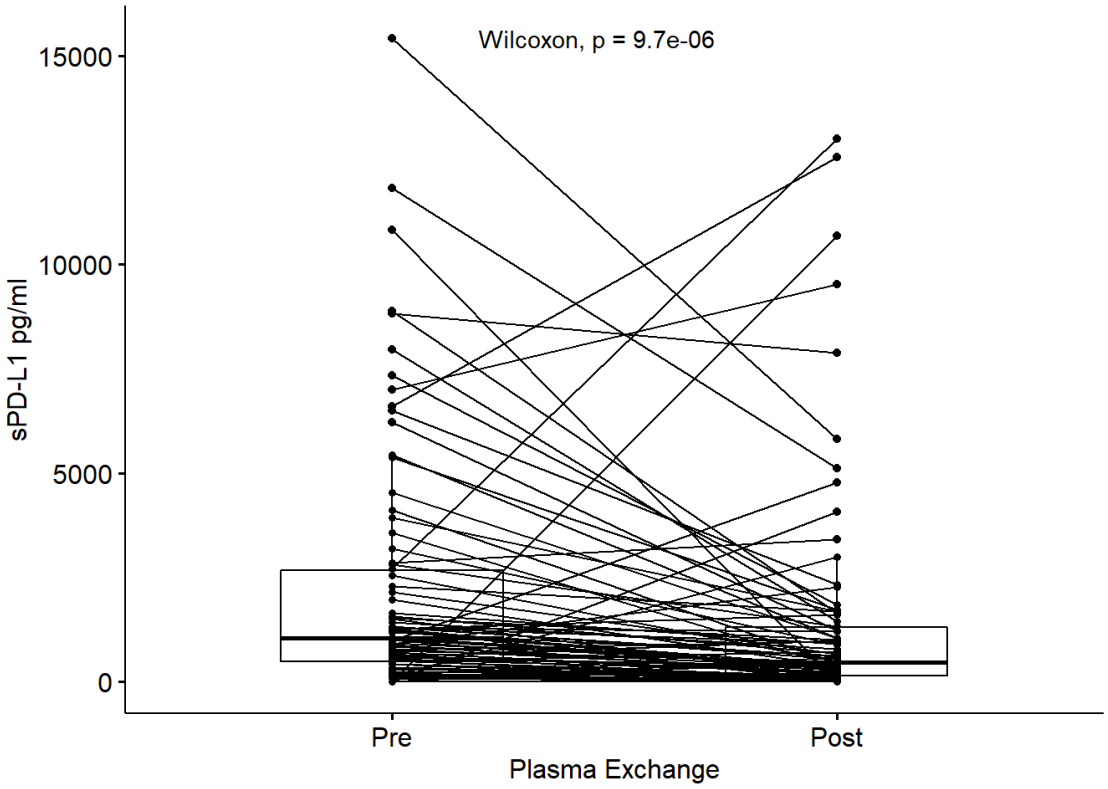

Patient 8
pg/ml sPD-L1
900
800
700
600
500
1
2
Treatment day
Patient 9
pg/ml sPD-L1
750
500
250
0
1 2 3 4 5 6 7 8
Treatment day
Patient 10
pg/ml sPD-L1
1000
500
0
1 2 3 4 5 6 7 8
Treatment day
Patient 11
pg/ml sPD-L1
1000
750
500
250
0
1 2 3 4 5 6
Treatment day
Patient 12
pg/ml sPD-L1
600
400
200
0
1 2 3 4 5 6 7
Treatment day
Patient 13
pg/ml sPD-L1
6000
5000
4000
3000
2000
1 2 3 4 5 6 7 8
Treatment day


Patient 14
pg/ml sPD-L1
Treatment day
Patient 15
pg/ml sPD-L1
Treatment day
Patient 16
pg/ml sPD-L1
Treatment day
Patient 17
pg/ml sPD-L1
Treatment day
Patient 18
pg/ml sPD-L1
Treatment day
Patient 19
pg/ml sPD-L1
Treatment day



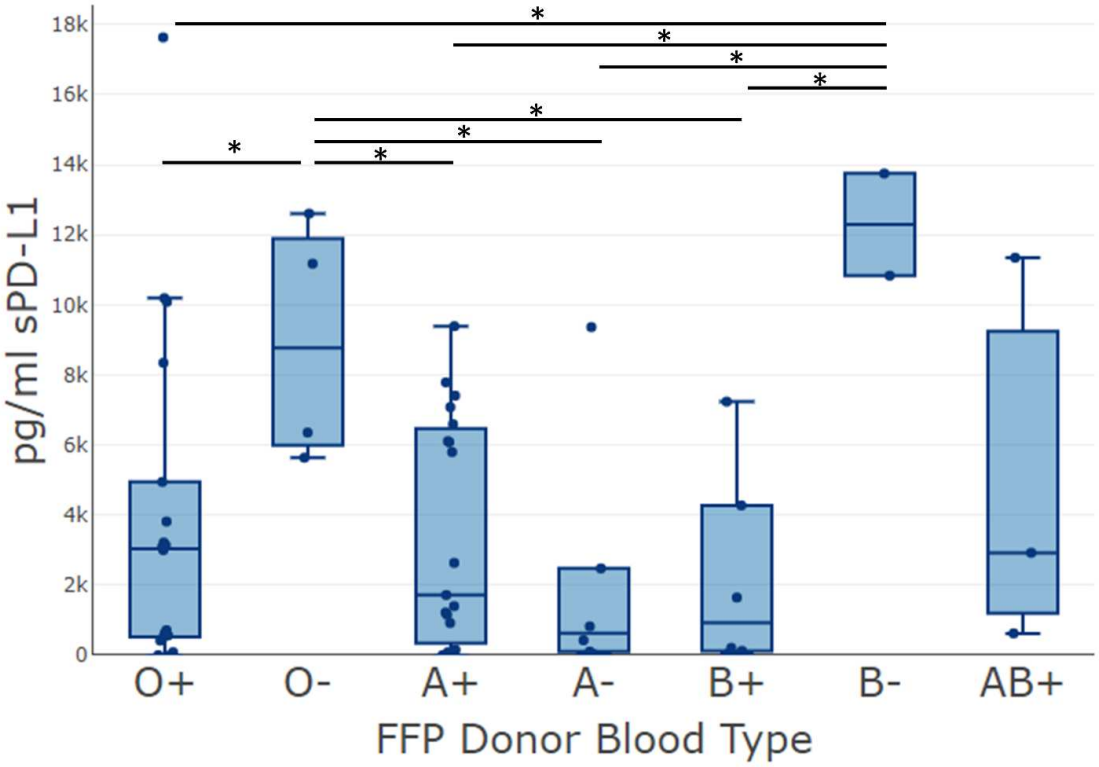
Supplemental Figure 2. Plasma sPD-L1 in all TPE treatment courses (including sessions involving FFP). Treatment courses of each patient are shown. Dark gray bars represent TPE sessions in which FFP was given. Light gray bars represent TPE sessions in which no FFP (*i.e.* only albumin) replacement was given. Patient 22 treatment course is shown in Fig 2D. Patient 6 was excluded for biotin use.

Supplemental Figure 3. Plasma sPD-L1 in all TPE treatment courses (including sessions requiring FFP).



Supplemental Figure 3. Plasma sPD-L1 in all TPE treatment courses (including sessions requiring FFP). TPE significantly reduced sPD-L1 levels in all sessions, including those in which patients received donor fresh frozen plasma (FFP).

Supplemental Figure 4. FFP donor sPD-L1 correlates with blood type.

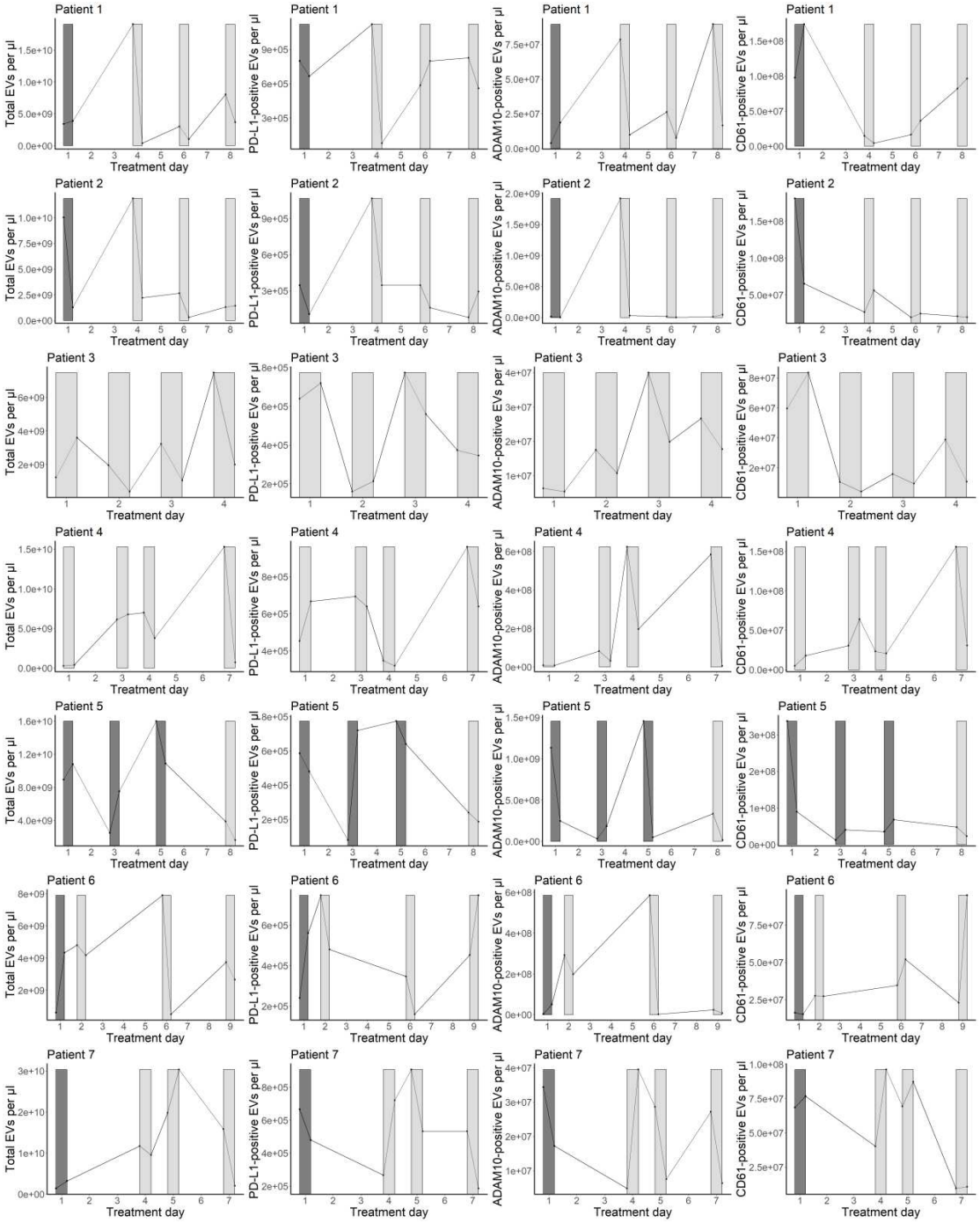


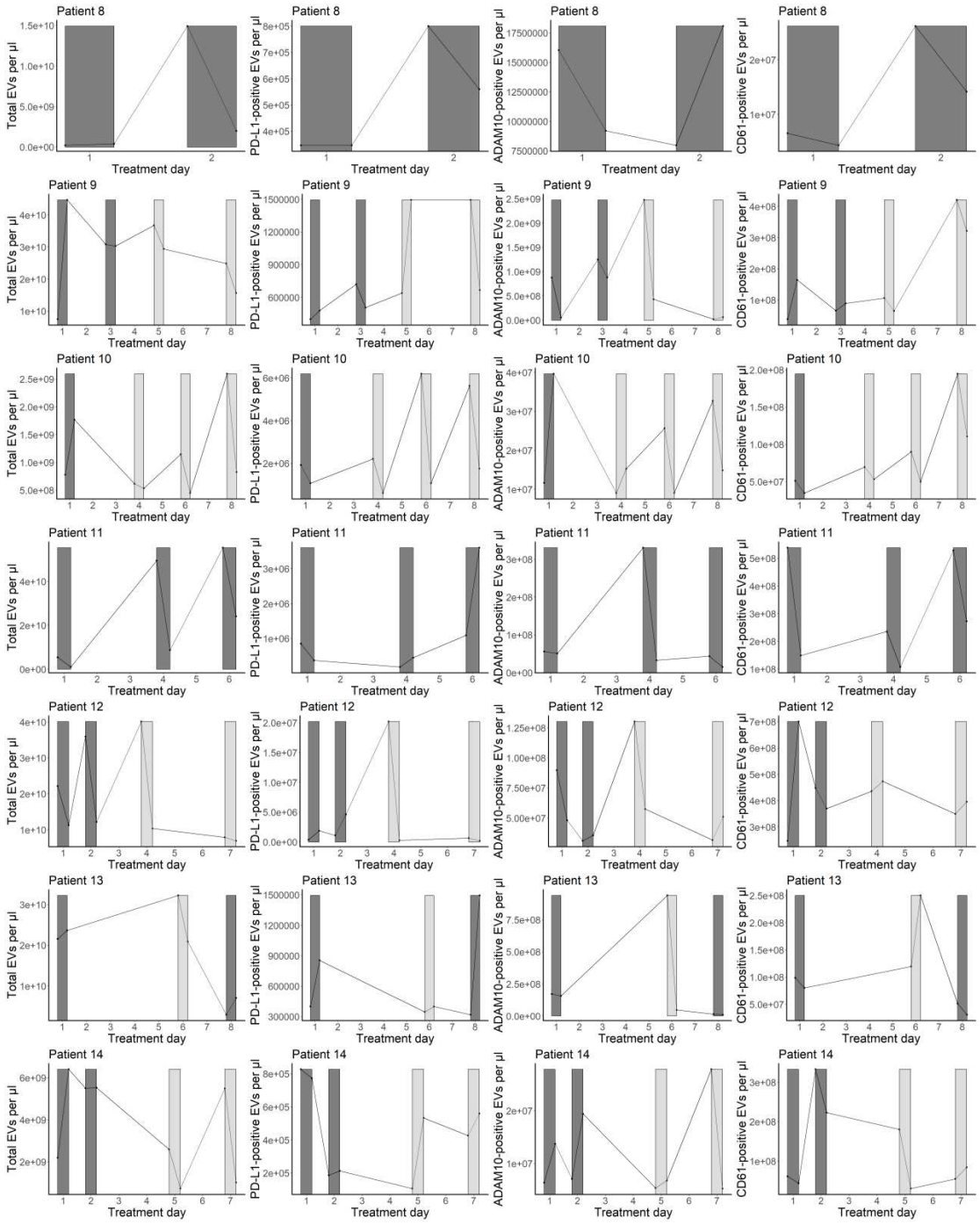
	P	mean	lower95CI	upper95CI
O+	0.05	3909	2051	5767
O-	1	8942	6093	11791
A+	0.04	3448	2207	4689
A-	0.02	2205	0	4636
B+	0.02	2258	293	4223
B-	0.22	12289	9890	14688
AB+	0.35	4963	0	10323

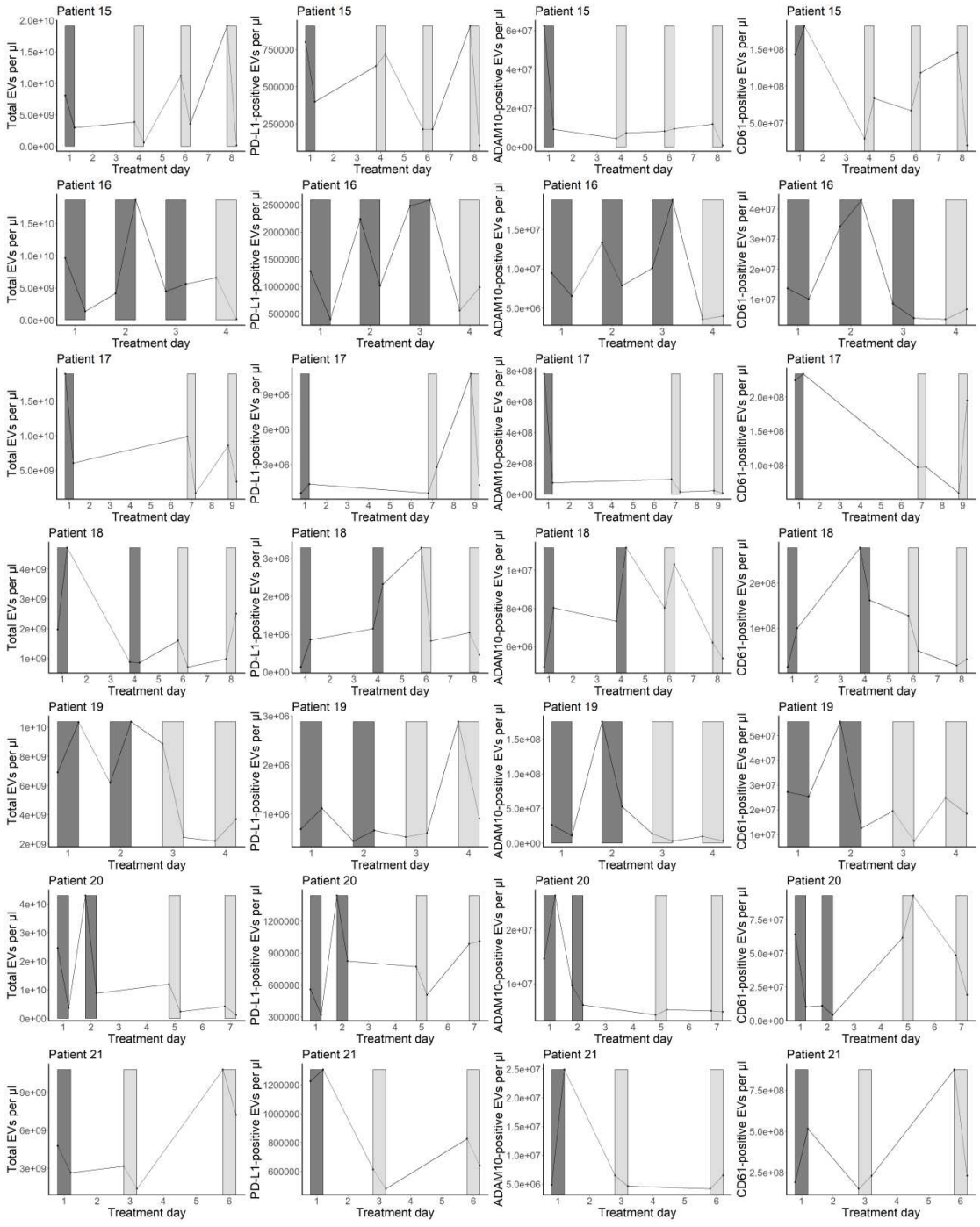
	p	mean	lower95CI	upper95CI
O+	0.03	3909	2051	5767
O-	0.22	8942	6093	11791
A+	0.05	3448	2207	4689
A-	0.01	2205	0	4636
B+	0.02	2258	293	4223
B-	1	12289	9890	14688
AB+	0.14	4963	0	10323

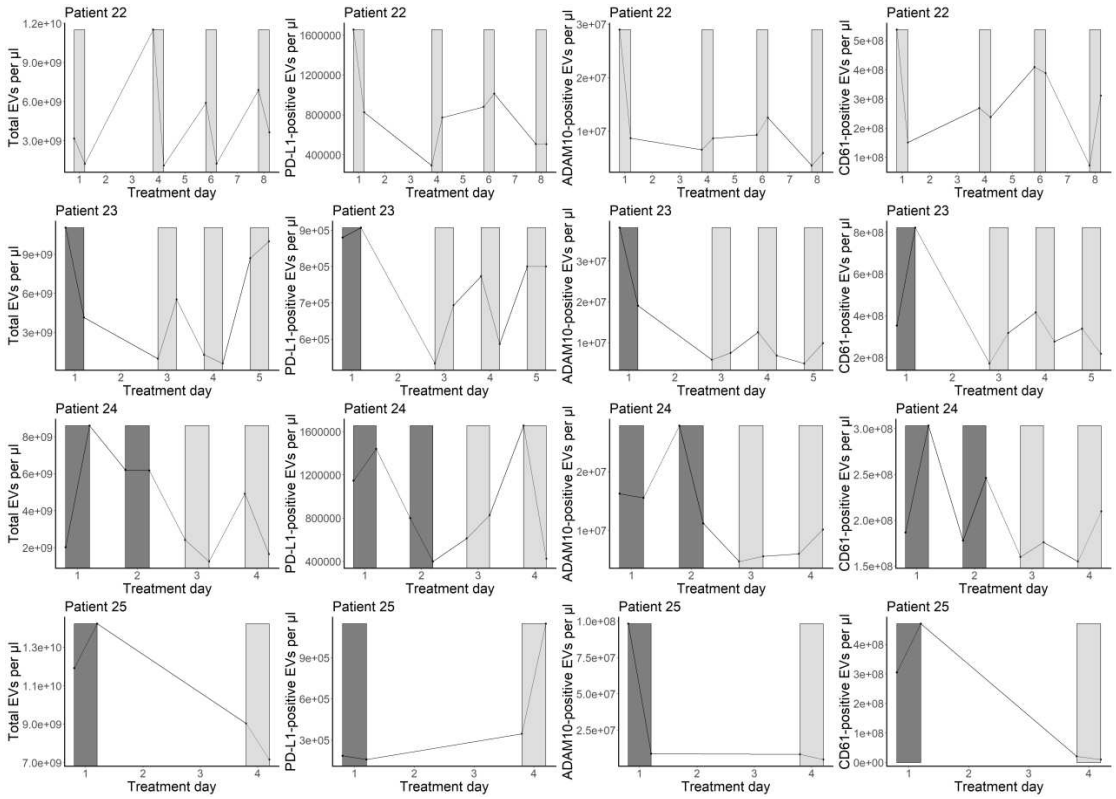
Supplemental Figure 4. FFP donor sPD-L1 correlates with blood type. Plasma from donors of fresh frozen plasma (FFP) showed variable levels of sPD-L1 by blood type.

Supplemental Figure 5. Plasma EVs in all TPE treatment courses (including sessions requiring FFP).



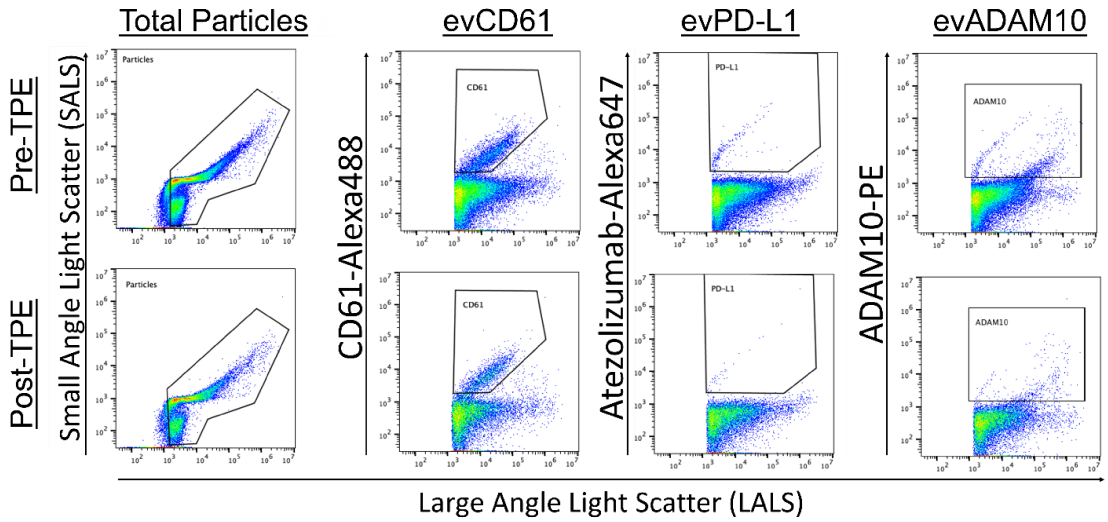

Patient 8
Patient 9
Patient 10
Patient 11
Patient 12
Patient 13
Patient 14
Total EVs per µl
PD-L1-positive EVs per µl
ADAM10-positive EVs per µl
CD61-positive EVs per µl
Treatment day


Patient 15
Patient 16
Patient 17
Patient 18
Patient 19
Patient 20
Patient 21
Total EVs per µl
PD-L1-positive EVs per µl
ADAM10-positive EVs per µl
CD61-positive EVs per µl
Treatment day



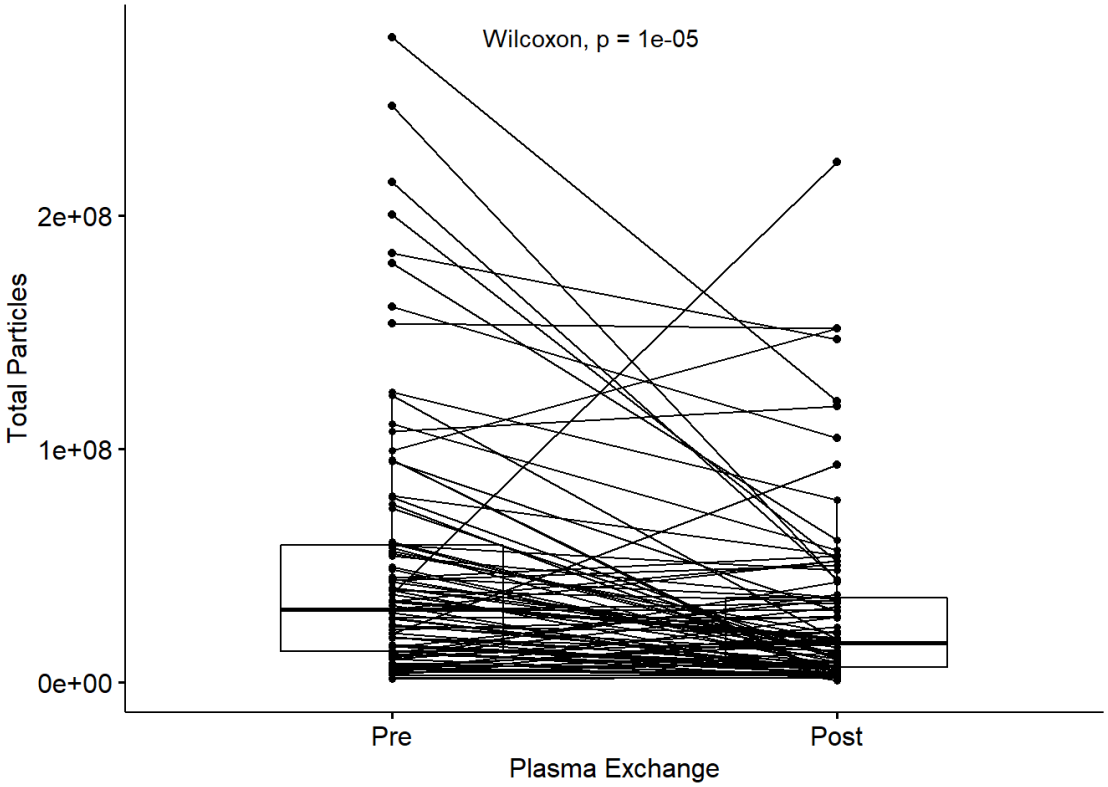
Supplemental Figure 5. Plasma EVs in all TPE treatment courses (including sessions requiring FFP). Plasma EV (total, PD-L1-positive, ADAM10-positive, and CD61-positive) levels over the course of TPE treatment are shown. Bars indicate TPE sessions, usually lasting 2 hours. Light-colored bars indicate that no FFP was received during the TPE session; conversely, dark bars indicate that FFP was received during the TPE session.

Supplemental Figure 6. Example plasma EV nanoflow plots.



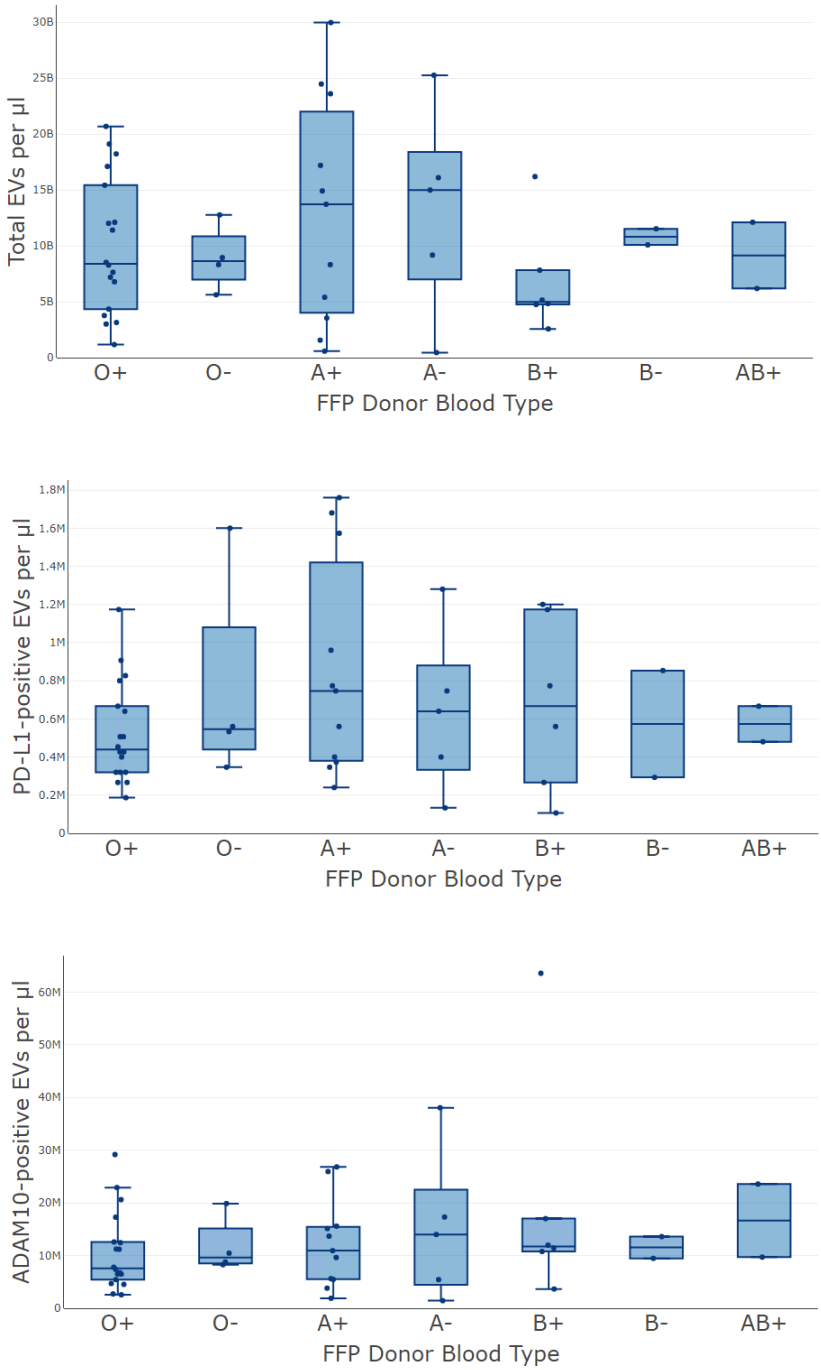
Supplemental Figure 6. Example plasma EV nanoflow plots. Patient 10 pre- (top row) and post- (bottom row) TPE nanoflow cytometry detecting total EVs, evCD61, evPD-L1, and evADAM10.

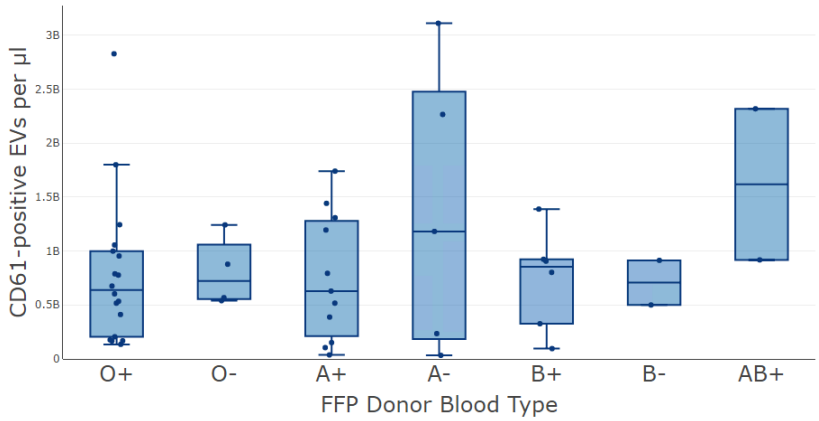
Supplemental Figure 7. Plasma EVs in all TPE treatment courses (including sessions requiring FFP).



Supplemental Figure 7. Plasma EVs in all TPE treatment courses (including sessions requiring FFP). Plasma total EV per microliter levels over the course of TPE treatment are shown including those sessions in which FFP was received.

Supplemental Figure 8. FFP donor EV concentrations do not correlate with blood type





Supplemental Figure 8. FFP donor EV concentrations do not correlate with blood type.