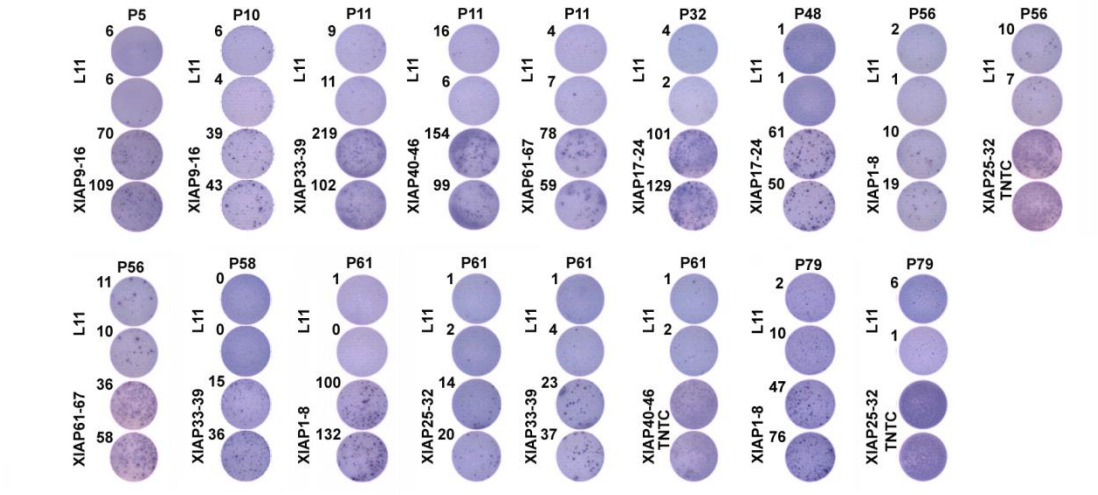
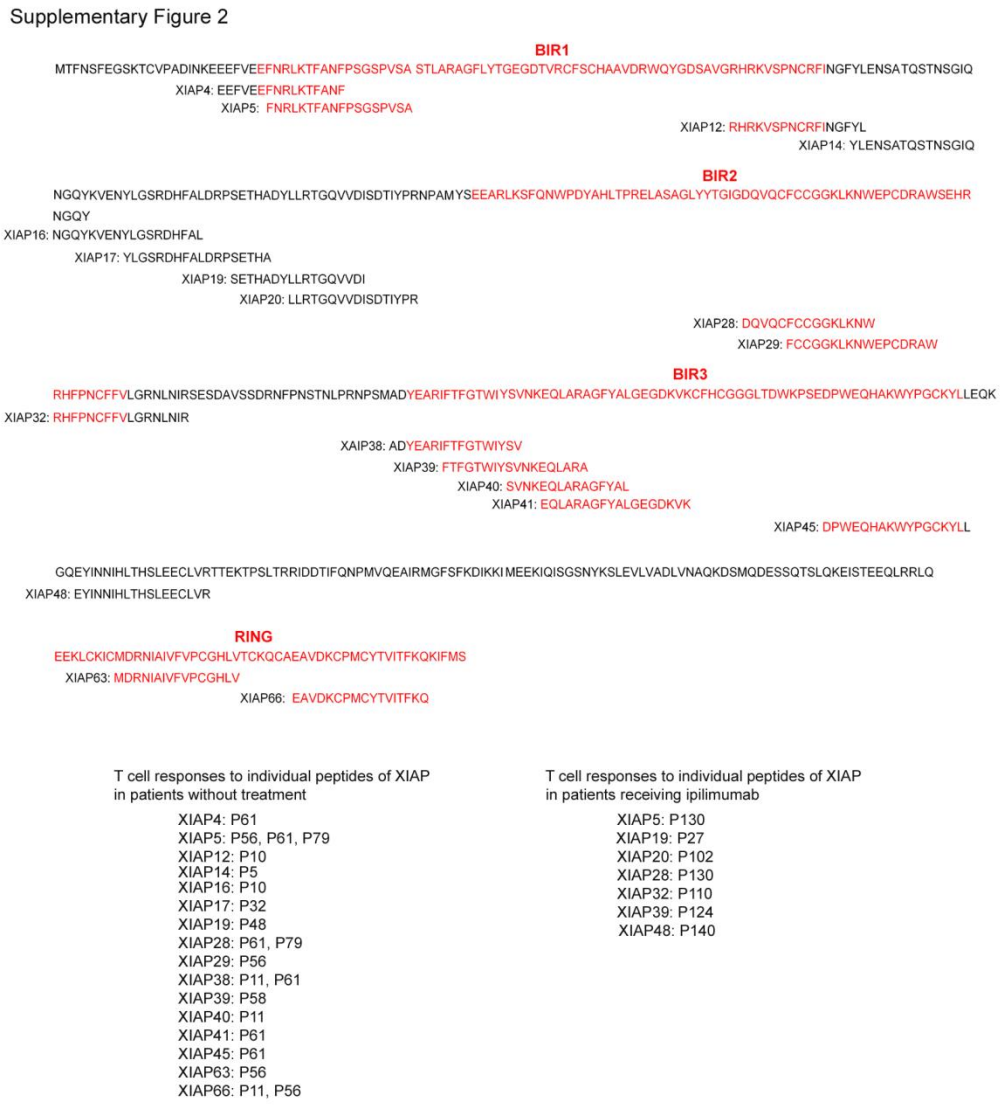
Supplementary Figure 1

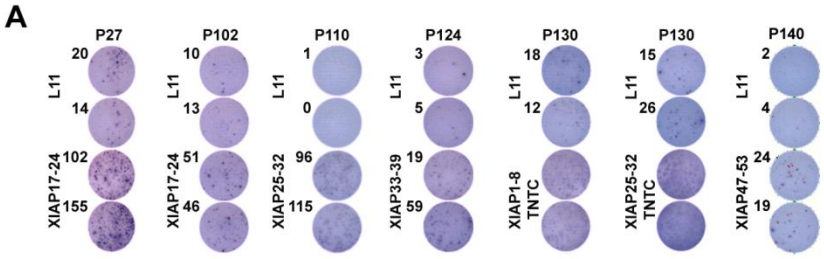


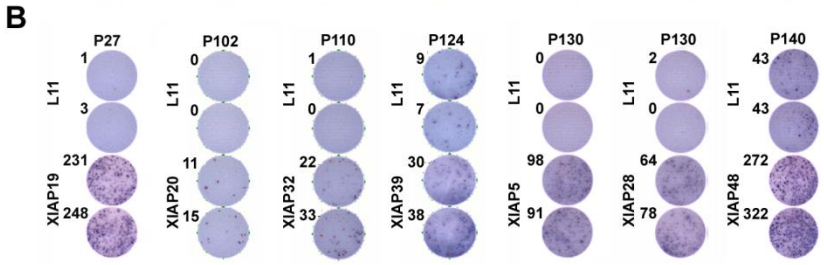
Supplementary Figure 1. T cell responses to peptide pools of XIAP in stage-IV melanoma patients using ELISPOT assays. TNTC: too numerous to count.



Supplementary Figure 2. Positions of XIAP peptides that induced T cell responses in the BIR domain and RING finger motifs of XIAP. BIR domains and RING finger motifs are indicated in red.

Supplementary Figure 3





C

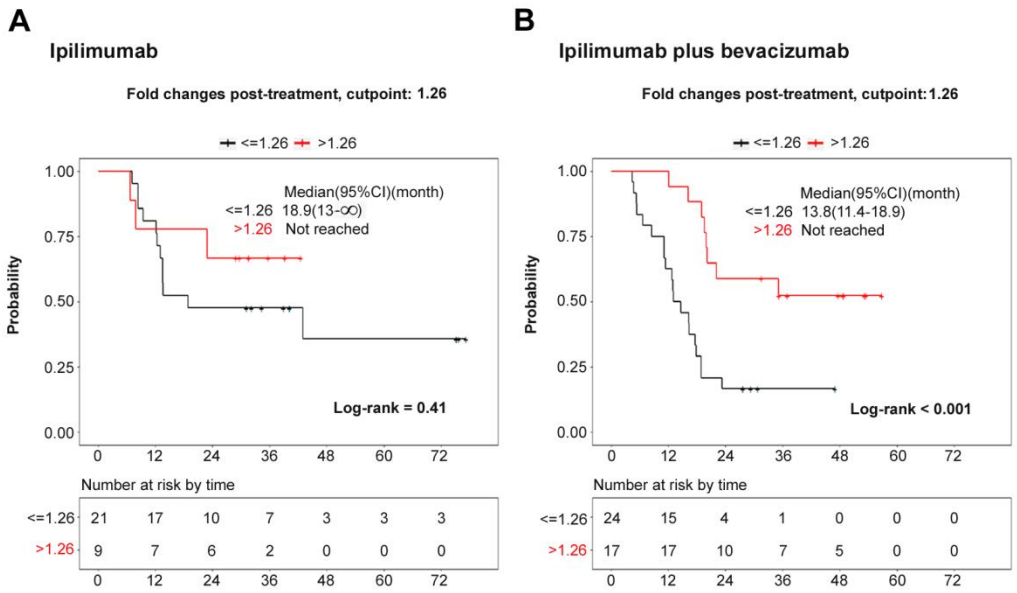
Comparisons in T cell responses to XIAP between untreated and ipilimumab-treated patients

Patients	untreated	ipilimumab-treated
Responders	9	6
Non-responders	26	1

Fisher exact test P = 0.005

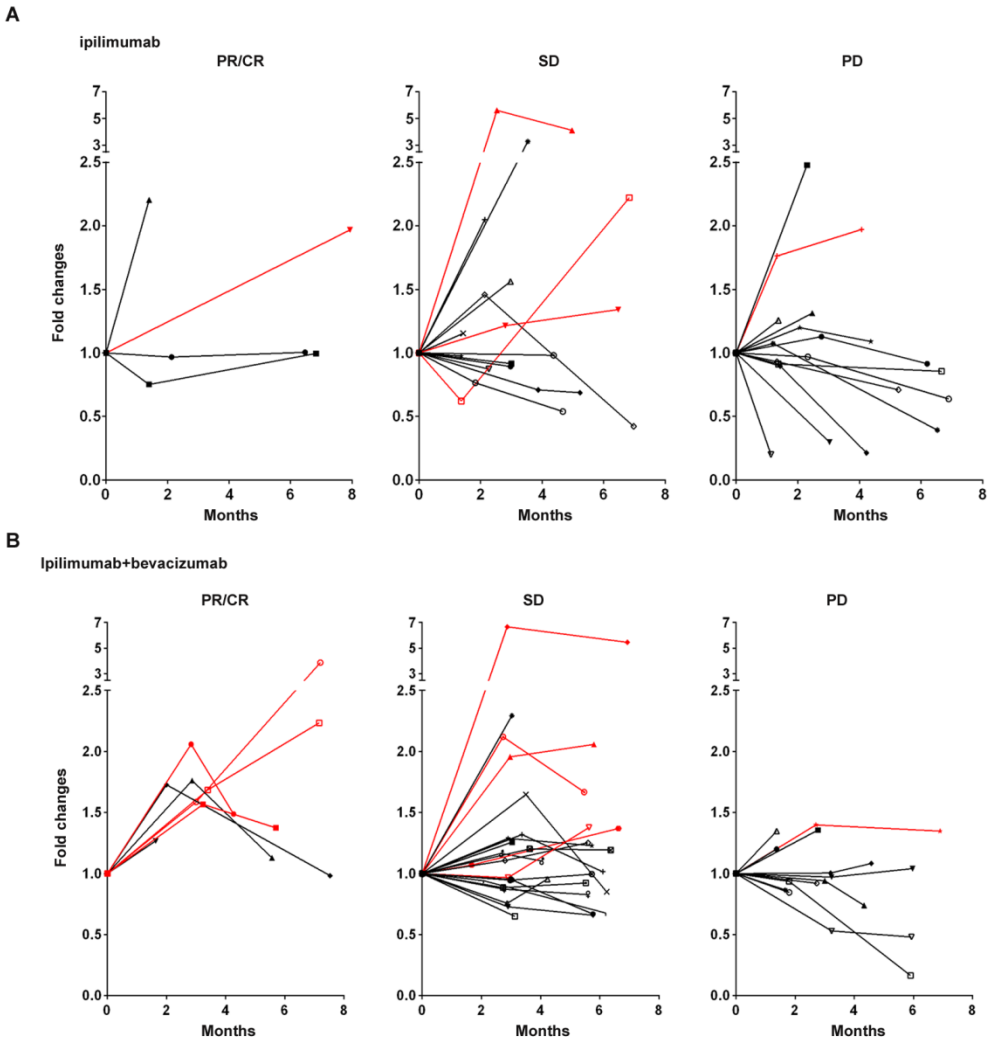
Supplementary Figure 3. T cell responses of melanoma patients to XIAP peptides following ipilimumab treatment. (A) T cell responses to peptide pools of XIAP in stage-IV melanoma patients following ipilimumab treatment using ELISPOT analyses. (B) T cell responses to individual peptides from the reactive peptide pools by ELISPOT analyses. (C) Comparisons of T cell responses to XIAP peptide pools between patients with and without ipilimumab treatment. Statistical comparisons were conducted using Fisher's exact tests. $P < 0.05$ was considered statistically significant.

Supplementary Figure 4



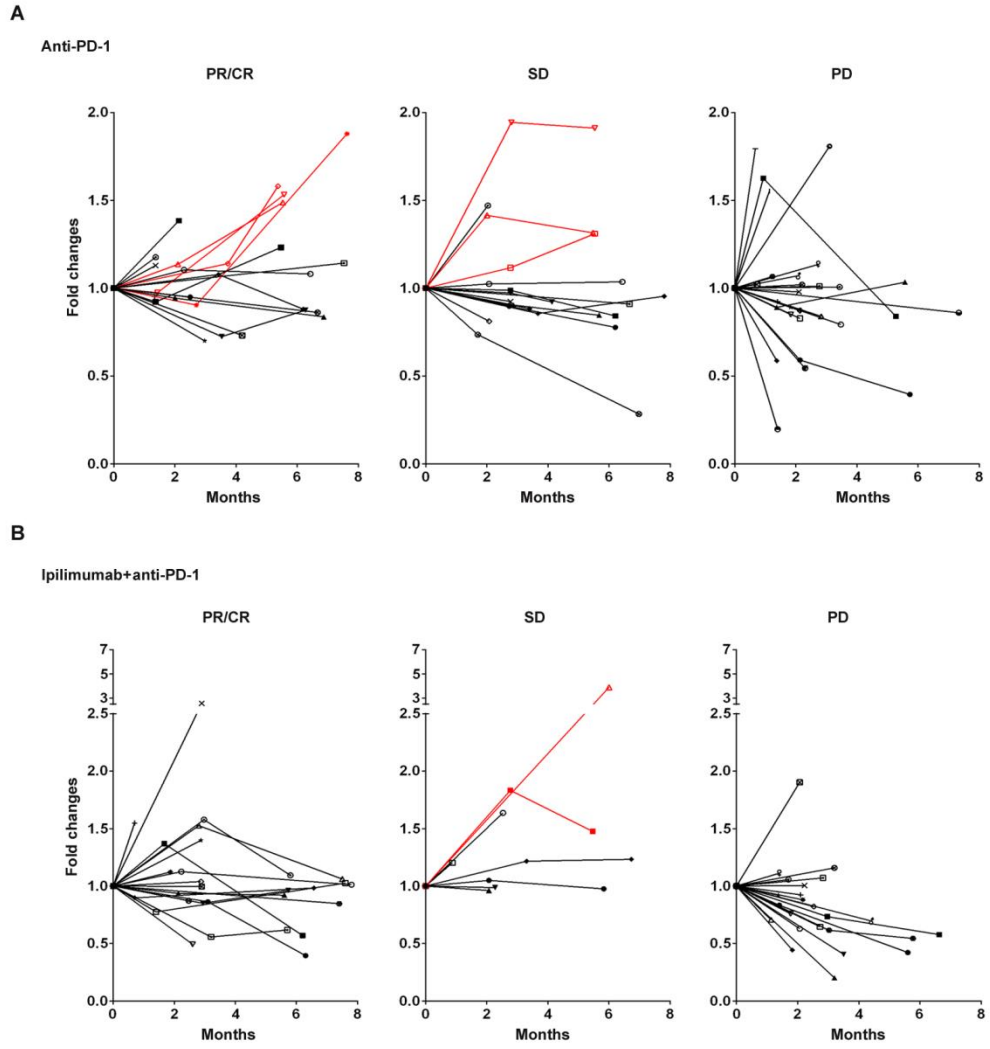
Supplementary Figure 4. Associations between survival and serologic responses to recombinant XIAP in melanoma patients receiving either (A) ipilimumab or (B) ipilimumab plus bevacizumab. Pre-treatment and post-treatment sera samples were examined by ELISA. Survival of high versus low fold-change (FC) groups were compared using stratified log-rank tests. $P < 0.05$ was considered statistically significant.

Supplementary Figure 5



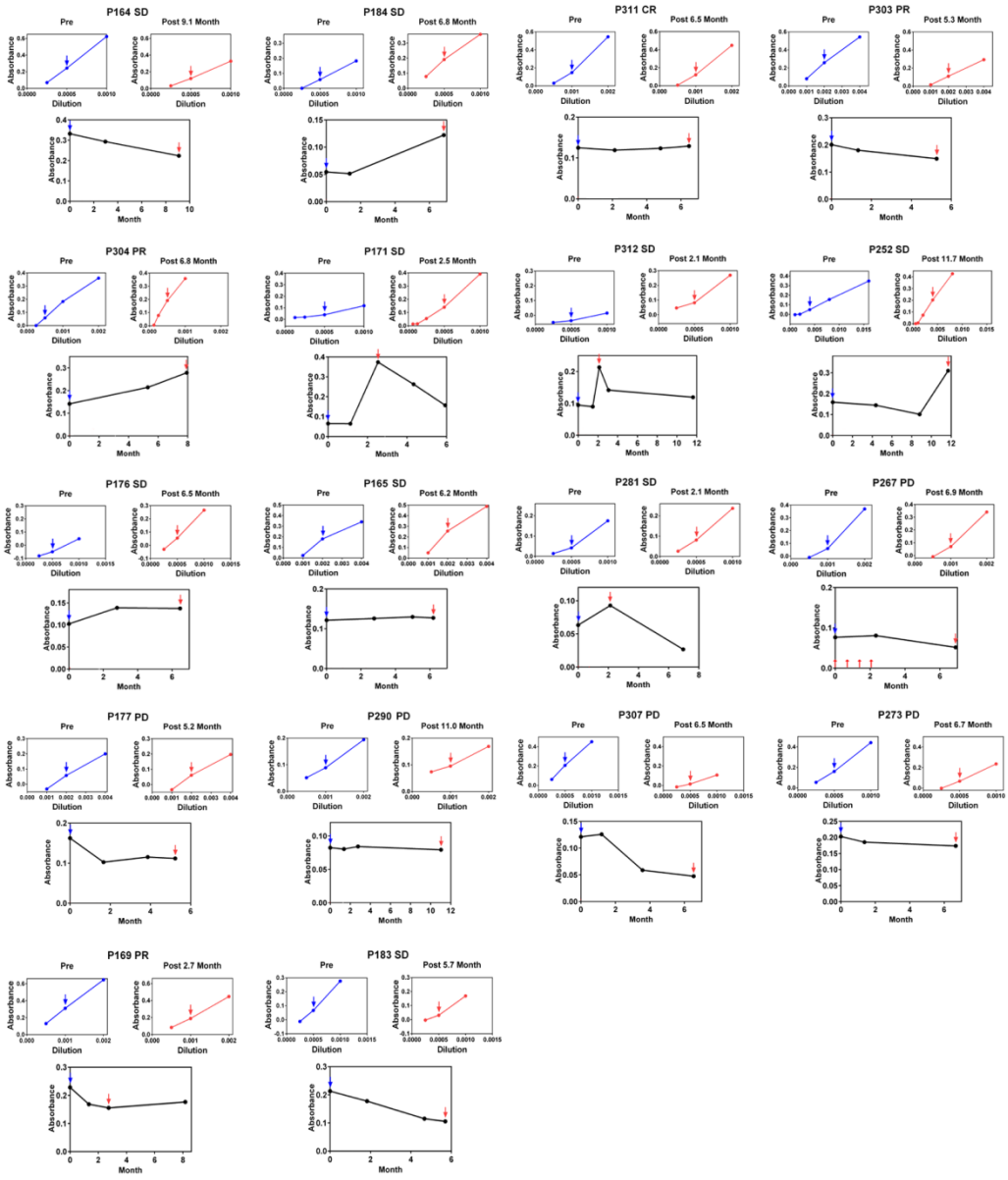
Supplementary Figure 5. Sera responses of melanoma patients to recombinant XIAP protein in patients receiving either ipilimumab or ipilimumab plus bevacizumab. Sera responses to recombinant XIAP proteins by ELISA. Long term/delayed increases in sera titers (after 4 months, > 1.26-fold change) are indicated in red.

Supplementary Figure 6



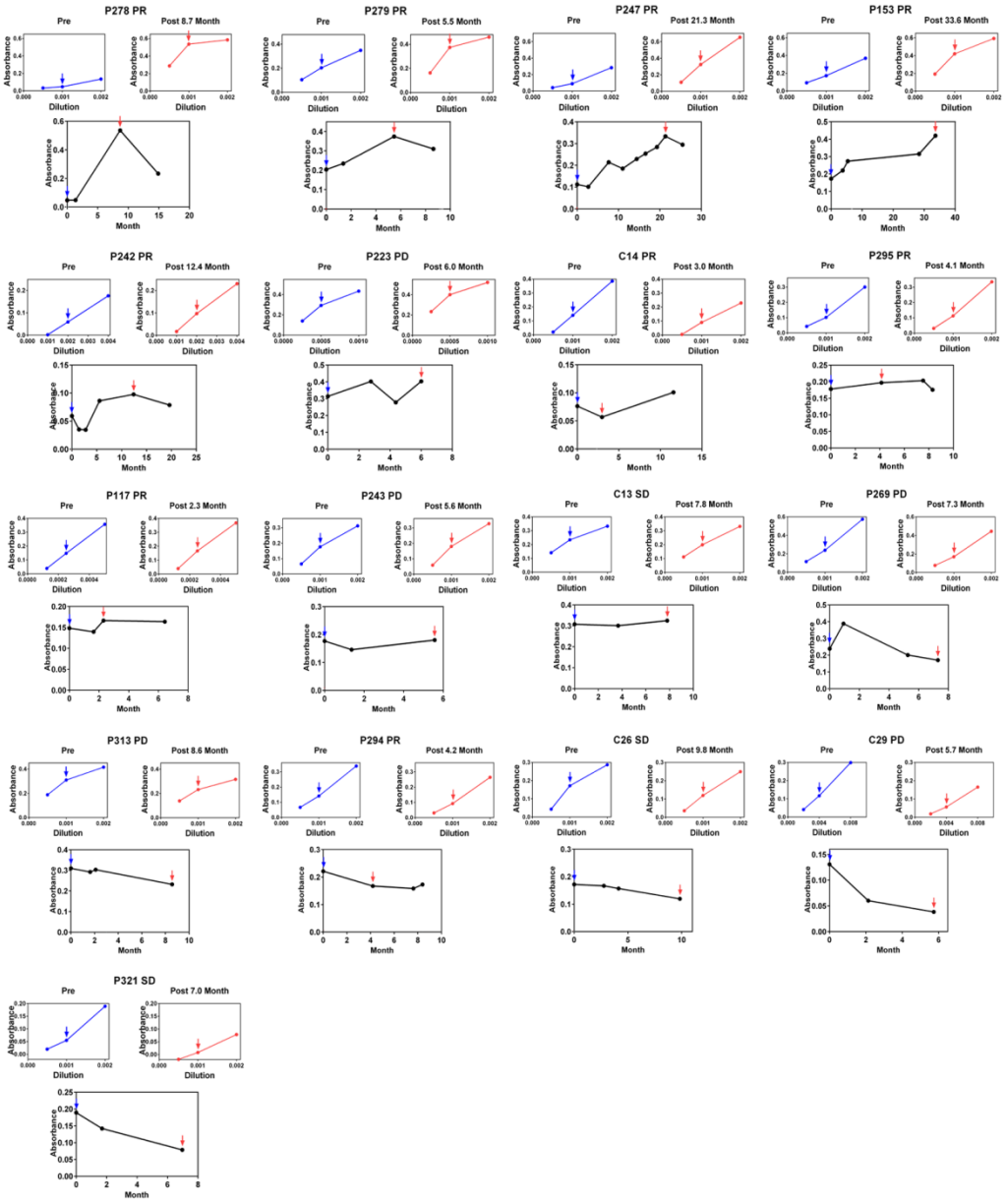
Supplementary Figure 6. Sera responses of melanoma patients to recombinant XIAP protein in patients receiving either anti-PD-1 or ipilimumab plus anti-PD-1. Sera responses to recombinant XIAP proteins by ELISA. Long term/delayed increases in sera titers (after 4 months, > 1.26-fold change) are indicated in red.

Supplementary Figure 7

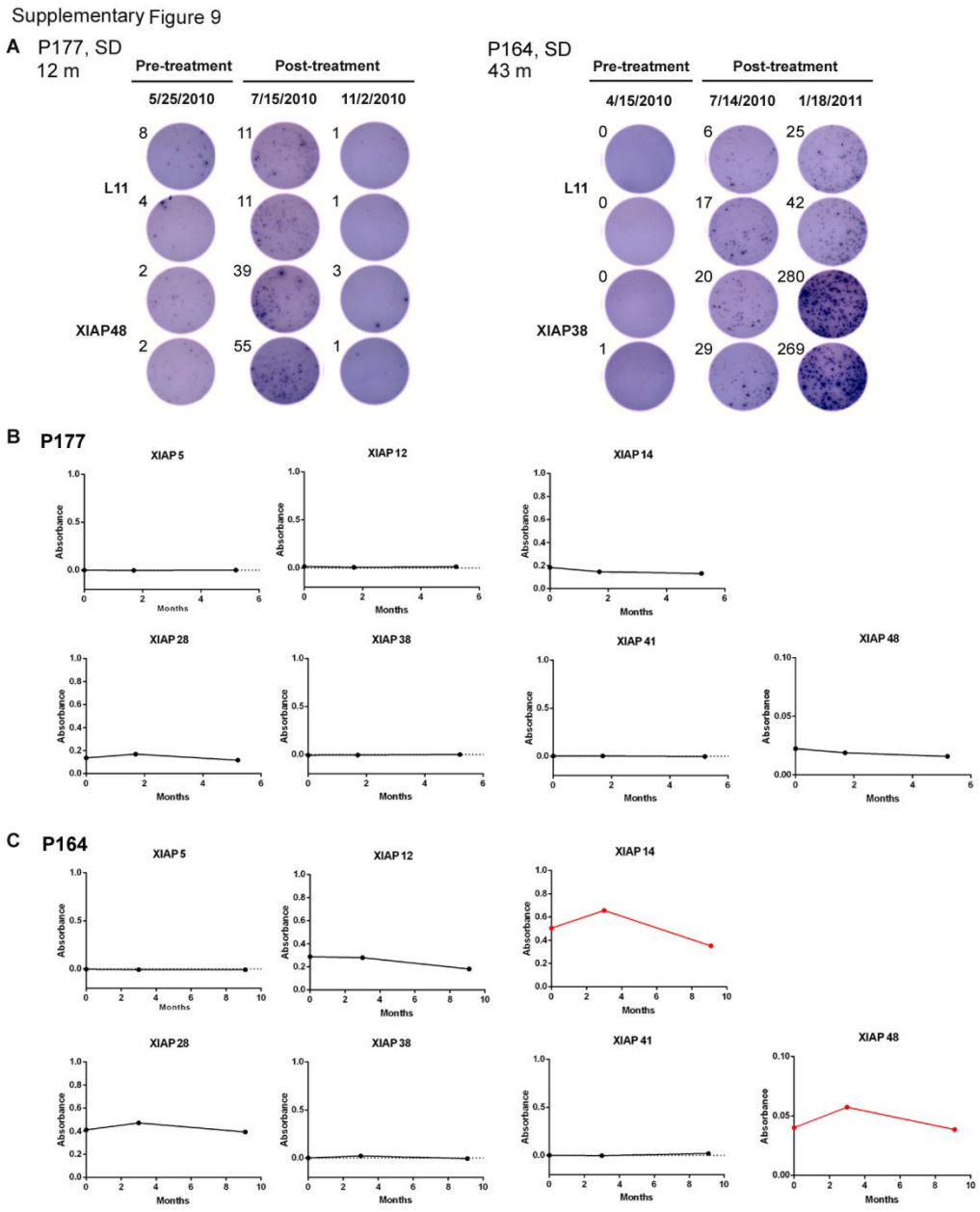


Supplementary Figure 7. Titration analyses of sera responses to XIAP by ELISA in patients receiving ipilimumab. Pre- or post-treatment time points of either lowest or highest sera responses to XIAP were chosen. Sera were prepared in a series of dilutions. Sera responses to XIAP at each time point were shown in a dose-dependent manner, and all sera concentrations titrated for ELISA were in dose responses range.

Supplementary Figure 8

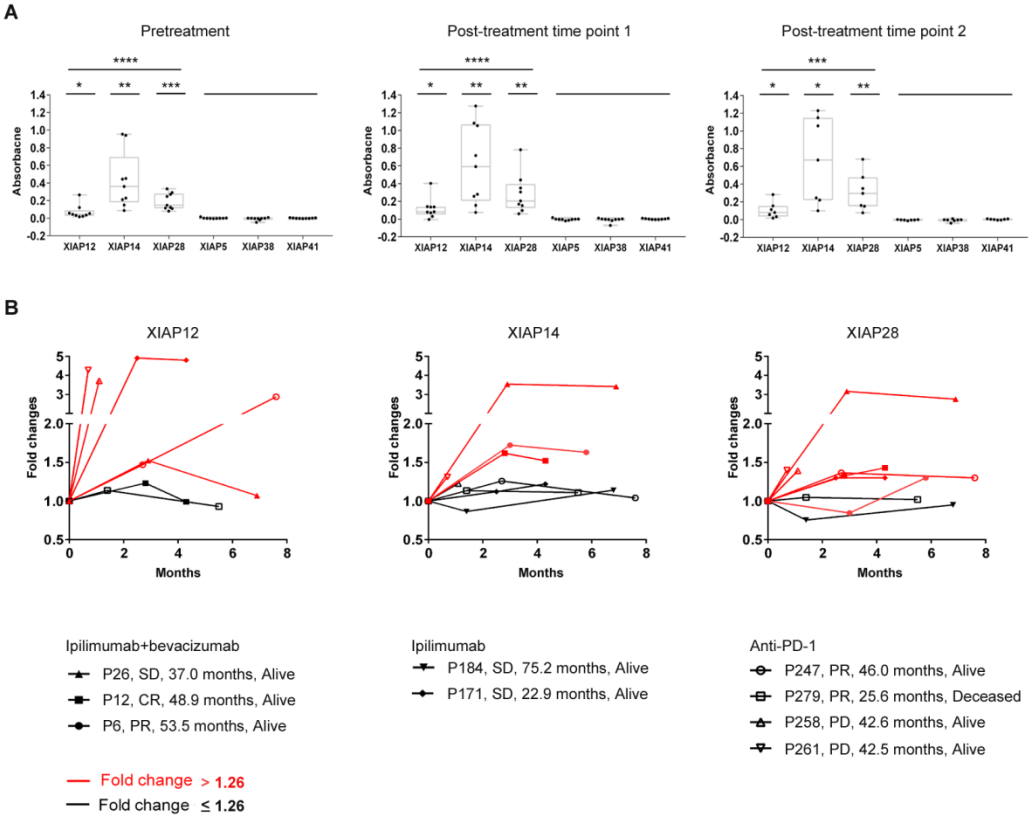


Supplementary Figure 8. Titration analyses of sera responses to XIAP by ELISA in patients receiving anti-PD-1. Pre- or post-treatment time points of either lowest or highest sera responses to XIAP were chosen. Sera were prepared in a series of dilution. Sera responses to XIAP at each time point were shown in a dose dependent manner, and all sera concentrations titrated for ELISA were in dose responses range.



Supplementary Figure 9. T cell and sera responses of melanoma patients P177 and P164 to XIAP peptides. (A) T cell responses to XIAP48 in patient P177 receiving ipilimumab, and T cell responses to XIAP38 in patient P164 receiving ipilimumab. TNTC: too numerous to count. M: month. (B) Sera titers to XIAP peptides at pre-treatment and post-treatment in patient P177. (C) Sera titer to XIAP peptides at pre-treatment and post-treatment of patient P164. Red line indicates greater than 1.26-fold increases after treatment.

Supplementary Figure 10



Supplementary Figure 10. Sera responses of melanoma patients to XIAP peptides. (A) Sera titers to XIAP peptides at pre-treatment and post-treatment with check-point blockade. (B) Kinetic changes of sera titer to XIAP peptides after check point blockade. Red lines indicate a greater than 1.26-fold increase after treatment.

Supplementary Table 1

Associations between fold-changes of sera titers and clinical response

A Ipilimumab-based treatment

	≤1.26	>1.26	Total
PD+SD	43	18	61
CR+PR	2	8	10

Fisher's exact test P=0.004

B Anti-PD-1 antibody

	≤1.26	>1.26	Total
PD+SD	34	8	42
CR+PR	14	1	15

Fisher's exact test P=0.42

C Ipilimumab plus anti-PD-1 antibody

	≤1.26	>1.26	Total
PD+SD	25	3	28
CR+PR	12	6	18

Fisher's exact test P=0.12

Supplementary Table 1. Associations between fold-changes of sera titers to XIAP peptides and clinical response in melanoma patients receiving: (A) ipilimumab-based treatment; (B) anti-PD-1; or, (C) ipilimumab plus anti-PD-1. Statistical comparisons used Fisher's exact tests. $P < 0.05$ was considered statistically significant.

Supplementary Table 2

Association between response to XIAP and sex or melanoma subtype

A. Ipilimumab-based treatment

	Unadjusted model		Adjusted model	
Covariates	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
XIAP fold-change (> 1.26 vs. <=1.26)	9.56 (1.85 – 49.46)	0.01	9.47 (1.82 – 49.36)	0.01
Sex (Male vs. Female)			0.65 (0.15 – 2.77)	0.56
Melanoma subtype (Cutaneous vs. Other)			0.69 (0.16 - 3.08)	0.63

B. Anti-PD-1 antibody

	Unadjusted model		Adjusted model	
Covariates	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
XIAP fold-change (> 1.26 vs. <=1.26)	0.30 (0.03-2.66)	0.28	0.27 (0.03 – 2.54)	0.25
Sex (Male vs. Female)			2.90 (0.76 – 11.14)	0.12
Melanoma subtype (Cutaneous vs. Other)			6.01 (0.68 – 52.86)	0.11

C. Ipilimumab plus anti-PD-1 antibody

	Unadjusted model		Adjusted model	
Covariates	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
XIAP fold-change (> 1.26 vs. <=1.26)	4.17 (0.89 - 19.58)	0.07	7.87 (0.79 – 78.46)	0.08
Sex (Male vs. Female)			2.22 (0.50 - 9.88)	0.29
Melanoma subtype (Cutaneous vs. Other)			470096363.43 (0.00 - Inf)	0.99

Supplementary Table 2. Associations of sex and melanoma subtype with response to XIAP based on logistic regression models. (A) ipilimumab-based treatment. (B) anti-PD-1. (C) ipilimumab plus anti-PD-1. $P < 0.05$ was considered statistically significant.

Supplementary Table 3

Association between overall survival and sex or melanoma subtype

A. Ipilimumab-based treatment

	Unadjusted model		Adjusted model	
Covariates	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
XIAP fold-change (> 1.26 vs. <=1.26)	0.38 (0.19 - 0.76)	<0.01	0.36 (0.18 - 0.72)	<0.01
Sex (Male vs. Female)			1.21 (0.65 - 2.24)	0.55
Melanoma subtype (Cutaneous vs. Other)			0.64 (0.34 - 1.20)	0.16

B. Anti-PD-1 antibody

	Unadjusted model		Adjusted model	
Covariates	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
XIAP fold-change (> 1.26 vs. <=1.26)	1.37 (0.51 - 3.68)	0.53	1.47 (0.55 - 3.98)	0.44
Sex (Male vs. Female)			0.52 (0.26 - 1.04)	0.07
Melanoma subtype (Cutaneous vs. Other)			0.54 (0.25 - 1.18)	0.12

C. Ipilimumab plus anti-PD-1 antibody

	Unadjusted model		Adjusted model	
Covariates	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
XIAP fold-change (> 1.26 vs. <=1.26)	0.36 (0.08 - 1.58)	0.18	0.40 (0.09 - 1.78)	0.23
Sex (Male vs. Female)			0.56 (0.19 - 1.67)	0.30
Melanoma subtype (Cutaneous vs. Other)			0.35 (0.13 - 0.94)	0.04

Supplementary Table 3. Association between overall survival and sex or melanoma subtype based on Cox proportional hazards regression. (A) Ipilimumab-based treatment. (B) Anti-PD-1. (C) Ipilimumab plus anti-PD-1. $P < 0.05$ was considered statistically significant.