

CHEK1 and BAP1 combination as a potential prognostic biomarker for pleural mesothelioma

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Objectives

BRCA1 associated protein (BAP1) was shown to be a predictive and putative prognostic biomarker for pleural mesothelioma. Checkpoint Kinase 1 protein (CHK1) is a DNA repair protein involved in chemotherapy resistance. We aimed to investigate whether a combination of BAP1 with CHK1 expression in tumor may have prognostic potential.

Methods

BAP1 loss (BAP1-) or retain (BAP1+) and CHK1 negative (CHK1-) or positive (CHK1+) expression was assessed by immunohistochemistry on slides of chemotherapy and immunotherapy naïve patients with pleural mesothelioma. CHK1 and BAP1 mouse monoclonal antibody were used. Sex, age, performance status, subtype, stage, and Charlson's comorbidity index were retrieved from medical records and registries. Overall survival (OS) was defined as time from histopathological diagnosis to date of death. For statistical analyses, Fisher's exact test, t-test, log-rank tests, Kaplan-Meier curves and univariate and multivariate Cox regression analyses were performed using STATA version 17. P-values < 0.05 were considered significant.

Results

In total, 100 patients were included. The OS was calculated for patients showing BAP1- or BAP1+ (Table 1, Figure 1a), CHK1- or CHK1+ (Table 1, Figure 1b) and combinations of BAP1 and CHK1 expressions (Table 1, Figure 1c). A significantly higher OS was observed in patients with BAP1- (17 months, 95%CI: 12-21, p < 0.05) versus BAP1+ (7 months, 95%CI: 4-10) and in those with BAP1-/CHK1+ (19 months, 95%CI: 13-24, p<0.01) versus BAP1-/CHK1- (13 months, 95%CI: 8-19), BAP1+/CHK1- (7 months, 95%CI: 2-11) and BAP1+/CHK1+ (5 months, 95%CI: 1-17). Patients with CHK1+ showed a trend in survival benefit (17 months, 95%CI: 11-21, p = 0.08) compared to those with CHK1- (10 months, 95%CI: 7-14) (Table 1, Figure 1b).

Conclusion

Combination of positive CHK1 and loss BAP1 expression may be a novel positive prognostic biomarker in pleural mesothelioma. Further validation is warranted.

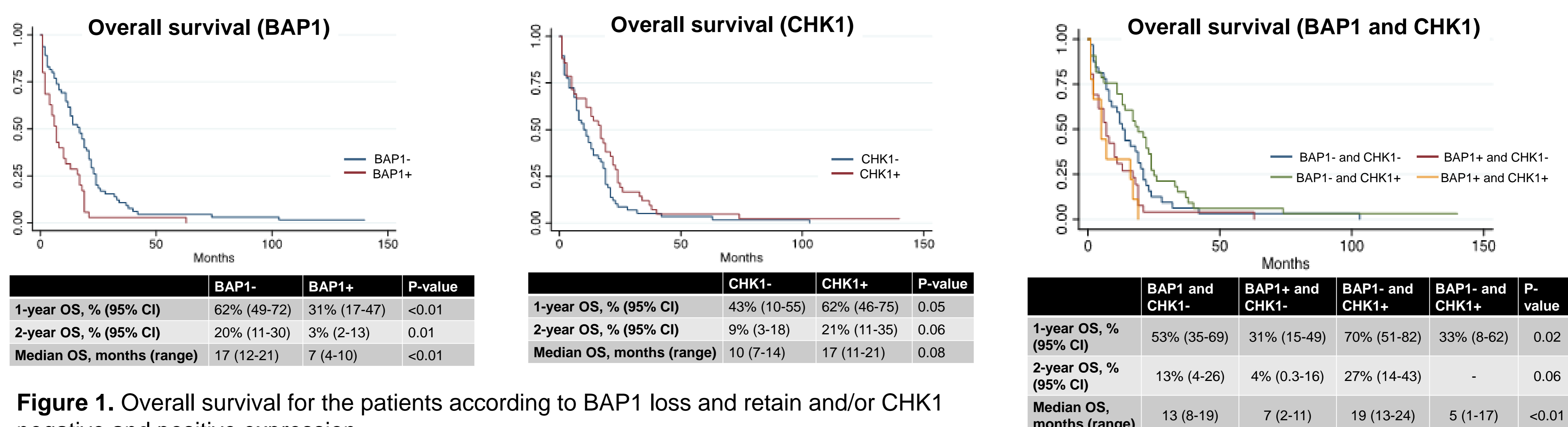


Figure 1. Overall survival for the patients according to BAP1 loss and retain and/or CHK1 negative and positive expression.

GROUPS	BAP1			CHK1			BAP1 and CHK1				
	BAP1- (N=65)	BAP1+ (N=35)	P-values	CHK1- (N=58)	CHK1+ (N=42)	P-values	BAP1- and CHK1- (N=32)	BAP1+ and CHK1- (N=26)	BAP1- and CHK1+ (N=33)	BAP1+ and CHK1+ (N=9)	P-values
Age, years, median (range)	65 (45-91)	72 (48-91)	0.06	67 (48-89)	68 (45-91)	0.67	64 (53-80)	73 (48-89)	66 (45-91)	68 (54-91)	NA
Sex											
Male	60	32	0.58	53	39	0.55	30	23	30	9	0.87
Female	5	3		5	3		2	3	3	0	
Subtype											
Epithelioid	31	17	0.71	28	20	0.85	14	14	17	3	0.90
Biphasic	23	12		21	14		13	8	10	4	
Sarcomatoid	4	4		5	3		2	3	2	1	
NA	7	2		4	5		3	1	4	1	
TNM stage											
I-III	42	27	0.41	39	30	0.37	18	21	24	6	0.34
IV	14	6		14	6		10	4	4	2	
NA	9	2		5	6		4	1	5	1	
Charlson's comorbidity index											
0-1	51	22	0.20	43	30	0.81	26	17	25	5	0.54
≥ 2	11	11		13	9		5	8	6	3	
NA	3	2		2	3		1	1	2	1	
Performance status											
0-1	47	22	0.38	39	30	0.77	23	16	24	6	0.87
≥ 2	9	9		12	6		5	7	4	2	
NA	9	4		7	6		4	3	5	1	
Median OS, months (95%CI)	17 (12-21)	7 (4-10)	< 0.01	10 (7-14)	17 (11-21)	0.08	13 (8-19)	7 (2-11)	19 (13-24)	5 (1-17)	< 0.01

Table 1. Clinical, pathological and survival information for the patients according to BAP1 loss or retain and CHK1 negative or positive expression.