

## ■ Sun-084 ■

## 레고라페닙 이전 시대에서 소라페닙 치료에 실패한 간세포암 환자의 생존예측인자 분석

고려대학교 구로병원 내과

\* 김동인, 이찬우, 이영선

**목적:** 소라페닙은 진행성 간세포암 환자의 일반 치료법이다. 하지만 상당수의 환자들이 진행, 부작용, 임상부전으로 소라페닙 치료의 실패를 경험한다. 우리는 예후 예측인자와 레고라페닙 이전 시대에서 소라페닙을 중단한 진행성 간세포암 환자들에게 second-line cytotoxic systemic chemotherapy (CSC) 가 미치는 역할 연구를 목표로 한다. **대상 및 방법:** 2007년에서 2015년까지 레고라페닙 이전 단계에서 영구적으로 소라페닙을 중단한 진행성 간세포암 환자 166명의 의무기록을 후향적으로 검토했다. 소라페닙 중단 사유로는 종양 진행, 부작용, 임상부전이 평가되었다. 소라페닙 치료 실패 후 생존요인에 대한 추가적 분석을 위해, best supportive care group (BSC) 와 selective best supportive care (SBSC) group 간의 second-line treatment 후 간 기능 유지 환자들의 생존을 비교하였다. **결과:** 소라페닙 중단 후, 전체 생존기간 중간값은 2.8개월(1.9-3.7)이었다. 부작용, 진행, 낮은 수준의 임상 조건에 의한 소라페닙 중단 환자들의 전체 생존기간은 각각 5.5개월(2.4-8.6), 5.5개월(2.2-8.9), 0.9개월(0.5-1.3)이었다( $p<0.001$ ). 소라페닙 실패 후 독립 생존예측인자는 혈청 수준의 벌리루빈과 알부민, 알파-페토프로테인, 중단 사인(discontinuation cause), second-line CSC 이었다. SCSC 집단과 BSC group 간의 생존을 비교할 경우, CSC 집단이 BCS group (10.6개월 vs 1.6개월,  $p<0.001$ ) 과 SBSC group(10.6개월 vs 4.2개월,  $p=0.023$ )보다 나은 생존 결과를 보였다. **결론:** 진행과 부작용으로 인한 소라페닙 중단 환자들의 소라페닙 실패 후 생존은 임상적 악화로 인해 치료를 중단한 환자들에 비해 훨씬 높은 것으로 나타났다. 레고라페닙 이전 단계의 경우, second-line CSC를 받은 환자들이 소라페닙 실패 후 supportive care만 받은 환자들 보다 높은 생존을 보였다.

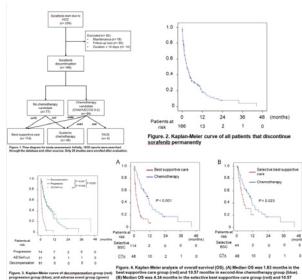


Figure 3. Kaplan-Meier curve of overall survival (OS) stratified by discontinuation cause. P < 0.001.

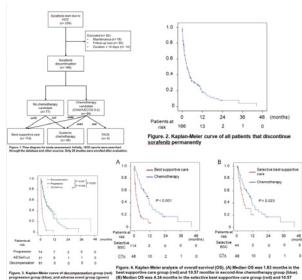


Figure 4. Kaplan-Meier analysis of overall survival (OS). (A) Median OS was 1.6 months in the best supportive care group and 10.6 months in the chemotherapy group. (B) Median OS was 0.9 months in the best supportive care group and 5.5 months in the chemotherapy group. P < 0.001.

Table 1. Baseline characteristics

Characteristic	BSC Group (n = 40)	CSC Group (n = 40)	P-value
Demographics			
Age (mean)	67.8 ± 10.1	68.4 ± 11.0	0.056
Male, n (%)	30 (75.0%)	30 (75.0%)	0.946
Marital status (%)			
Married	100 (100%)	100 (100%)	-
Alcohol	22 (22.0%)	16 (16.0%)	0.066
Tobacco	12 (12.0%)	10 (10.0%)	0.302
HCV	11 (11.0%)	10 (10.0%)	0.910
Others	11 (11.0%)	12 (12.0%)	0.810
Others	5 (5.0%)	5 (5.0%)	0.000
Performance status (%)			
0	13 (32.5%)	13 (32.5%)	0.373
1	27 (67.5%)	27 (67.5%)	-
ECOG performance status (%)			
0	10 (25.0%)	10 (25.0%)	0.370
1	30 (75.0%)	30 (75.0%)	-
GFR as initial therapy, n (%)			
≥ 60 mL/min	34 (85.0%)	34 (85.0%)	0.994
< 60 mL/min	6 (15.0%)	6 (15.0%)	-
Initial treatment, n (%)			
SBSC	16 (40.0%)	16 (40.0%)	0.990
SCSC	24 (60.0%)	24 (60.0%)	-
Other	0 (0.0%)	0 (0.0%)	-
Albumin, g/dL	5.3 ± 0.6	5.3 ± 0.6	0.996
PT, sec	13.4 ± 3.4	13.4 ± 3.4	0.996
APTT, sec	35.0 ± 10.0	35.0 ± 10.0	0.996
Alb/PT ratio, n (%)			
≥ 1.0	27 (67.5%)	27 (67.5%)	0.997
< 1.0	13 (32.5%)	13 (32.5%)	-
Vascular invasion, n (%)			
No	30 (75.0%)	30 (75.0%)	0.997
Yes	10 (25.0%)	10 (25.0%)	-
Disease progression, n (%)			
No	10 (25.0%)	10 (25.0%)	0.996
Yes	30 (75.0%)	30 (75.0%)	-
Disease progression, n (%)			
No	14 (35.0%)	14 (35.0%)	0.996
Yes	26 (65.0%)	26 (65.0%)	-
Reason for discontinuation, n (%)			
Side effect	17 (42.5%)	17 (42.5%)	0.996
Progression	12 (30.0%)	12 (30.0%)	-
Other	11 (27.5%)	11 (27.5%)	-
Discontinuation reason, n (%)			
Side effect	11 (27.5%)	11 (27.5%)	0.996
Progression	10 (25.0%)	10 (25.0%)	-
Other	14 (37.5%)	14 (37.5%)	-
Table 2. Univariate and multivariate analysis for survival factors after discontinuation of osimertinib			

Table 3. Comparison between best supportive care group and chemotherapy group

Characteristic	BSC Group (n = 40)	CSC Group (n = 40)	P-value
Demographics			
Age (mean)	67.8 ± 10.1	68.4 ± 11.0	0.056
Male, n (%)	30 (75.0%)	30 (75.0%)	0.946
Marital status (%)			
Married	100 (100%)	100 (100%)	-
Alcohol	22 (22.0%)	16 (16.0%)	0.066
Tobacco	12 (12.0%)	10 (10.0%)	0.302
HCV	11 (11.0%)	10 (10.0%)	0.910
Others	11 (11.0%)	12 (12.0%)	0.810
Others	5 (5.0%)	5 (5.0%)	0.000
Performance status (%)			
0	13 (32.5%)	13 (32.5%)	0.373
1	30 (75.0%)	30 (75.0%)	-
ECOG performance status (%)			
0	10 (25.0%)	10 (25.0%)	0.370
1	30 (75.0%)	30 (75.0%)	-
GFR as initial therapy, n (%)			
≥ 60 mL/min	34 (85.0%)	34 (85.0%)	0.994
< 60 mL/min	6 (15.0%)	6 (15.0%)	-
Initial treatment, n (%)			
SBSC	16 (40.0%)	16 (40.0%)	0.990
SCSC	24 (60.0%)	24 (60.0%)	-
Other	0 (0.0%)	0 (0.0%)	-
Albumin, g/dL	5.3 ± 0.6	5.3 ± 0.6	0.996
PT, sec	13.4 ± 3.4	13.4 ± 3.4	0.996
APTT, sec	35.0 ± 10.0	35.0 ± 10.0	0.996
Alb/PT ratio, n (%)			
≥ 1.0	27 (67.5%)	27 (67.5%)	0.997
< 1.0	13 (32.5%)	13 (32.5%)	-
Vascular invasion, n (%)			
No	30 (75.0%)	30 (75.0%)	0.997
Yes	10 (25.0%)	10 (25.0%)	-
Disease progression, n (%)			
No	10 (25.0%)	10 (25.0%)	0.996
Yes	30 (75.0%)	30 (75.0%)	-
Reason for discontinuation, n (%)			
Side effect	17 (42.5%)	17 (42.5%)	0.996
Progression	12 (30.0%)	12 (30.0%)	-
Other	11 (27.5%)	14 (37.5%)	-
Table 4. Response rates after 2 <sup>nd</sup> line chemotherapy			

Table 5. Summary of chemotherapy-related adverse events

Characteristic	Response	Total 48 patients
Best response rate	0 (%)	-
Complete response	0 (0.0)	-
Partial response	10 (20.8)	-
Stable disease	14 (29.2)	-
Disease progression	16 (33.3)	-
Not available	8 (16.7)	-
Objective response rate	10 (20.8)	-
Disease control rate	24 (50.0)	-
Grade 3 or 4 adverse events		
Adverse event	Any grade (n=48)	Grade 3 or 4
GI bleeding	2 (4.2%)	2 (4.2%)
Arterial embolism	1 (2.1%)	1 (2.1%)
Neutropenia	23 (47.9%)	23 (47.9%)
Vomiting	7 (14.6%)	7 (14.6%)
Abdominal pain	27 (56.3%)	27 (56.3%)
Abdominal distension	5 (10.4%)	5 (10.4%)
Diarrhea	31 (64.6%)	31 (64.6%)
Abnormal laboratory findings		
Neutrophil count	2 (4.2%)	2 (4.2%)
Platelet count	1 (2.1%)	1 (2.1%)
AST	1 (2.1%)	1 (2.1%)
ALT	1 (2.1%)	1 (2.1%)
Globulin	2 (4.2%)	2 (4.2%)
Albumin	1 (2.1%)	1 (2.1%)
Urea nitrogen	1 (2.1%)	1 (2.1%)
Creatinine	1 (2.1%)	1 (2.1%)
Chloride	1 (2.1%)	1 (2.1%)
Glucose	1 (2.1%)	1 (2.1%)
Na	1 (2.1%)	1 (2.1%)
K	1 (2.1%)	1 (2.1%)
Ca	1 (2.1%)	1 (2.1%)
bilirubin	1 (2.1%)	1 (2.1%)
SGOT	1 (2.1%)	1 (2.1%)
SGPT	1 (2.1%)	1 (2.1%)
Alkaline phosphatase	1 (2.1%)	1 (2.1%)
LDH	1 (2.1%)	1 (2.1%)
Urea nitrogen	1 (2.1%)	1 (2.1%)
Creatinine	1 (2.1%)	1 (2.1%)
Chloride	1 (2.1%)	1 (2.1%)
Glucose	1 (2.1%)	1 (2.1%)
Na	1 (2.1%)	1 (2.1%)
K	1 (2.1%)	1 (2.1%)
Ca	1 (2.1%)	1 (2.1%)
bilirubin	1 (2.1%)	1 (2.1%)
SGOT	1 (2.1%)	1 (2.1%)
SGPT	1 (2.1%)	1 (2.1%)
Alkaline phosphatase	1 (2.1%)	1 (2.1%)
LDH	1 (2.1%)	1 (2.1%)
Urea nitrogen	1 (2.1%)	1 (2.1%)
Creatinine	1 (2.1%)	1 (2.1%)
Chloride	1 (2.1%)	1 (2.1%)
Glucose	1 (2.1%)	1 (2.1%)
Na	1 (2.1%)	1 (2.1%)
K	1 (2.1%)	1 (2.1%)
Ca	1 (2.1%)	1 (2.1%)
bilirubin	1 (2.1%)	1 (2.1%)
SGOT	1 (2.1%)	1 (2.1%)
SGPT	1 (2.1%)	1 (2.1%)
Alkaline phosphatase	1 (2.1%)	1 (2.1%)
LDH	1 (2.1%)	1 (2.1%)
Urea nitrogen	1 (2.1%)	1 (2.1%)
Creatinine	1 (2.1%)	1 (2.1%)
Chloride	1 (2.1%)	1 (2.1%)
Glucose	1 (2.1%)	1 (2.1%)
Na	1 (2.1%)	1 (2.1%)
K	1 (2.1%)	1 (2.1%)
Ca	1 (2.1%)	1 (2.1%)
bilirubin	1 (2.1%)	1 (2.1%)
SGOT	1 (2.1%)	1 (2.1%)
SGPT	1 (2.1%)	1 (2.1%)
Alkaline phosphatase	1 (2.1%)	1 (2.1%)
LDH	1 (2.1%)	1 (2.1%)
Urea nitrogen	1 (2.1%)	1 (2.1%)
Creatinine	1 (2.1%)	1 (2.1%)
Chloride	1 (2.1%)	1 (2.1%)
Glucose	1 (2.1%)	1 (2.1%)
Na	1 (2.1%)	1 (2.1%)
K	1 (2.1%)	1 (2.1%)
Ca	1 (2.1%)	1 (2.1%)
bilirubin	1 (2.1%)	1 (2.1%)
SGOT	1 (2.1%)	1 (2.1%)
SGPT	1 (2.1%)	1 (2.1%)
Alkaline phosphatase	1 (2.1%)	1 (2.1%)
LDH	1 (2.1%)	1 (2.1%)
Urea nitrogen	1 (2.1%)	1 (2.1%)
Creatinine	1 (2.1%)	1 (2.1%)
Chloride	1 (2.1%)	1 (2.1%)
Glucose	1 (2.1%)	1 (2.1%)
Na	1 (2.1%)	1 (2.1%)
K	1 (2.1%)	1 (2.1%)
Ca	1 (2.1%)	1 (2.1%)
bilirubin	1 (2.1%)	1 (2.1%)
SGOT	1 (2.1%)	1 (2.1%)
SGPT	1 (2.1%)	1 (2.1%)
Alkaline phosphatase	1 (2.1%)	1 (2.1%)
LDH	1 (2.1%)	1 (2.1%)
Urea nitrogen	1 (2.1%)	1 (2.1%)
Creatinine	1 (2.1%)	1 (2.1%)
Chloride	1 (2.1%)	1 (2.1%)
Glucose	1 (2.1%)	1 (2.1%)
Na	1 (2.1%)	1 (2.1%)
K	1 (2.1%)	1 (2.1%)
Ca	1 (2.1%)	1 (2.1%)
bilirubin	1 (2.1%)	1 (2.1%)
SGOT	1 (2.1%)	1 (2.1%)
SGPT	1 (2.1%)	1 (2.1%)
Alkaline phosphatase	1 (2.1%)	1 (2.1%)
LDH	1 (2.1%)	1 (2.1%)
Urea nitrogen	1 (2.1%)	1 (2.1%)
Creatinine	1 (2.1%)	1 (2.1%)
Chloride	1 (2.1%)	1 (2.1%)
Glucose	1 (2.1%)	1 (2.1%)
Na	1 (2.1%)	1 (2.1%)
K	1 (2.1%)	1 (2.1%)
Ca	1 (2.1%)	1 (2.1%)
bilirubin	1 (2.1%)	1 (2.1%)
SGOT	1 (2.1%)	1 (2.1%)
SGPT	1 (2.1%)	1 (2.1%)
Alkaline phosphatase	1 (2.1%)	1 (2.1%)
LDH	1 (2.1%)	1 (2.1%)
Urea nitrogen	1 (2.1%)	1 (2.1%)
Creatinine	1 (2.1%)	1 (2.1%)
Chloride	1 (2.1%)	1 (2.1%)
Glucose	1 (2.1%)	1 (2.1%)
Na	1 (2.1%)	1 (2.1%)
K	1 (2.1%)	1 (2.1%)
Ca	1 (2.1%)	1 (2.1%)
bilirubin	1 (2.1%)	1 (2.1%)
SGOT	1 (2.1%)	1 (2.1%)
SGPT	1 (2.1%)	1 (2.1%)
Alkaline phosphatase	1 (2.1%)	1 (2.1%)
LDH	1 (2.1%)	1 (2.1%)
Urea nitrogen	1 (2.1%)	1 (2.1%)
Creatinine	1 (2.1%)	1 (2.1%)
Chloride	1 (2.1%)	1 (2.1%)
Glucose	1 (2.1%)	1 (2.1%)
Na	1 (2.1%)	1 (2.1%)
K	1 (2.1%)	1 (2.1%)
Ca	1 (2.1%)	1 (2.1%)
bilirubin	1 (2.1%)	1 (2.1%)
SGOT	1 (2.1%)	1 (2.1%)
SGPT	1 (2.1%)	1 (2.1%)
Alkaline phosphatase	1 (2.1%)	1 (2.1%)
LDH	1 (2.1%)	1 (2.1%)
Urea nitrogen	1 (2.1%)	1 (2.1%)
Creatinine	1 (2.1%)	1 (2.1%)
Chloride	1 (2.1%)	1 (2.1%)
Glucose	1 (2.1%)	1 (2.1%)
Na	1 (2.1%)	1 (2.1%)
K	1 (2.1%)	1 (2.1%)
Ca	1 (2.1%)	1 (2.1%)
bilirubin	1 (2.1%)	1 (2.1%)
SGOT	1 (2.1%)	1 (2.1%)
SGPT	1 (2.1%)	1 (2.1%)
Alkaline phosphatase	1 (2.1%)	1 (2.1%)
LDH	1 (2.1%)	1 (2.1%)
Urea nitrogen	1 (2.1%)	1 (2.1%)
Creatinine	1 (2.1%)	1 (2.1%)
Chloride	1 (2.1%)	1 (2.1%)
Glucose	1 (2.1%)	1 (2.1%)
Na	1 (2.1%)	1 (2.1%)
K	1 (2.1%)	1 (2.1%)
Ca	1 (2.1%)	1 (2.1%)
bilirubin	1 (2.1%)	1 (2.1%)
SGOT	1 (2.1%)	1 (2.1%)
SGPT	1 (2.1%)	1 (2.1%)</td