33 ROLE OF PLASMA T-CELL-DERIVED CIRCULATING DNA LEVEL IN ANTI-PD(L)1 IMMUNOTHERAPY IN ADVANCED STAGE NON-SMALL CELL LUNG CANCER

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Background We previously published prognostic impact of T-cell-derived circulating DNA (T-cirDNA) and its correlation with intra-tumoral CD8 tumor-infiltrating lymphocyte (TIL) in advanced stage non-small cell lung cancer (NSCLC). Currently, PD-L1 staining is solely the standard biomarker of anti-PD-(L)1 immunotherapy treatment response. However, not perfect correlation in individual patient.

Methods We prospectively explored plasma T-cirDNA and cirDNA (total circulating DNA), using real-time PCR with Taqman assay-specific rearranged TCR-beta CDR3 region in 47 advanced NSCLC patients treated with anti-PD-(L)1 immunotherapy. We defined patients into undetectable, low (≤1% ratio) and high (>1% ratio) T-cirDNA/cirDNA based on previous study. Demographic characteristics such as sex, age, ECOG performance status, smoking, histology, PD-L1 staining, treatment regimen were integrated with T-cirDNA/cirDNA into the cox-regression analysis model.

Results Out of 47 patients, 60% of participants had detectable plasma T-cirDNA/cirDNA with a median of 0.03 [range 0–4.7] ngml^{-1}(table 1). Undetectable group was significantly correlated with the longest overall survival (OS) with a median of 25.5 [range 8–73.7] months (p-value 0.05) (figure 1). Multivariate analysis of progression-free survival (PFS) revealed 0–1 ECOG performance status and undetectable T-cirDNA correlated with favorable outcome, hazard ratio (HR) of 0.05 [95% CI 0.007–0.4, p-value 0.005] and 0.1 [95% CI 0.01–0.7, p-value 0.02] respectively. High amount of circulating DNA which represented high tumor burden and mono-anti-PD-(L)1 immunotherapy were correlated with unfavorable disease control with the HR of 6.6 [95% CI 1.1–37.9, p-value 0.03] and 6.3 [95% CI 1.3–29.1, p-value 0.01] respectively. For detectable T-cirDNA group, high level correlated with better disease control than low level (HR 0.1 [95% CI 0.02–0.8, p-value 0.03]) (table 2). We did observe paradoxical effect in predictive implication in undetectable and high level of T-cirDNA/cirDNA%ratio.

Conclusions Incorporate with demographic characteristic, T-cell-derived circulating DNA could be adopted for predictive implication of anti-PD(L)1 immunotherapy usage.

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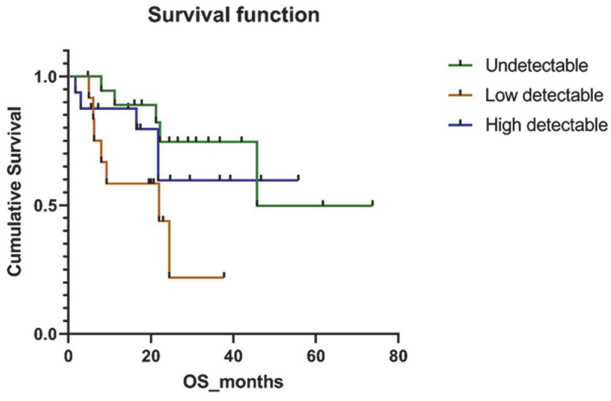
Ethics Approval All methods were carried out in accordance with the declarations of Helsinki. The Institutional Review Board (IRB), Faculty of Medicine, Chulalongkorn University approved the study protocol (IRB 385/63).

Abstract 33 Table 1 Demographic characteristics of detectable plasma circulating DNA from 47 advanced NSCLC patients categorized by%ratio of T-cirDNA/cirDNA into undetectable, low (≤ 1%ratio) and high (> 1%ratio)

Demographic characteristic	Undetectable T-cirDNA/cirDNA (%) (n=18)	Low detectable T-cirDNA/cirDNA (%) (n=13)	High detectable T-cirDNA/cirDNA (%) (n=16)	p value
Sex				0.909
Male	13(72.22)	10(76.92)	13(81.25)	
Female	5(27.78)	3(23.08)	3(18.75)	
Age at diagnosis				0.489
<60 years	3(16.67)	1(7.69)	4(25.00)	
≥60 years	15(83.33)	12(93.31)	12(75.00)	
ECOG performance status				0.720
0-1	15(83.33)	12(93.31)	15(93.75)	
>2	3(16.67)	1(7.69)	1(6.25)	
Smoking status				0.337
Never	6(33.33)	4(30.77)	2(12.50)	
Former/Current smoker	12(66.67)	9(69.23)	14(87.50)	
Histology				0.398
Adenocarcinoma	16(88.89)	12(93.31)	12(75.00)	
Non-adenocarcinoma	2(11.11)	1(7.69)	4(25.00)	
Driver alteration (EGFR/ALK)				1.000
Present	1(5.56)	0(0.00)	0(0.00)	
Absent	17(94.44)	13(100.00)	16(100.00)	
PD-L1 staining				0.464
Positive	3(16.67)	6(46.15)	5(31.25)	
Negative	7(38.89)	2(15.39)	4(25.00)	
Missing data	8(44.44)	5(38.46)	7(43.75)	
No. of lines of treatment				0.179
<2 lines	2(11.11)	5(38.46)	5(31.25)	
≥2 lines	16(88.89)	8(61.54)	11(68.75)	
Total amount of cirDNA				0.030*
High(>4.5 ngml^{-1})	11(61.11)	13(100.00)	13(81.25)	
Low(≤4.5 ngml^{-1})	7(38.89)	0(0.00)	3(18.75)	
Total amount of cirDNA				
RPP30, median (range)	6.71 (0-18.08)	27.18 (8.25-52.37)	14.54 (0.00-120.57)	0.000*
TCRβ, median (range)	0.00 (0.00-0.00)	0.08 (0.00-0.32)	0.47 (0.01-41.37)	0.000*
Therapy				0.423
Single I/O	14(77.78)	7(53.85)	11(68.75)	
Combined I/O	4(22.22)	6(46.15)	5(31.25)	
Response to I/O				0.944
Complete/ Partial response	5(27.78)	2(15.38)	4(25.00)	
Stable disease	5(27.78)	4(30.77)	4(25.00)	
Progression disease	8(44.44)	7(53.85)	8(50.00)	
PFS months, median (range)	3.75(0.50-28.25)	3.00(0.75-8.25)	3.63(0.75-19.25)	0.727
OS months, median (range)	25.50(8.00-73.75)	19.50(4.75-37.75)	19.63(1.75-55.75)	0.050*



Abstract 33 Figure 1 A cumulative survival curve comparison of% ratio of T-cirDNA/cirDNA; undetectable, low and high by using overall survival (Kaplan–Meier method and Log rank test, p-value 0.071)

Abstract 33 Table 2 Univariate and multivariate analysis of prognostic factors by progression-free survival including demographic characteristics, treatment and%ratio of T-cirDNA/cirDNA using cox proportion hazards regression analysis

Variables	Univariate, HR [95% CI]	p value	Multivariate, HR [95% CI]	p value
Sex (male vs. female)	0.730 [0.363-1.471]	0.379	1.266 [1.390-11.537]	0.835
Age (< 60 vs. ≥ 60)	1.954 [0.877-4.355]	0.101	2.246 [0.557-9.054]	0.255
ECOG (0–1 vs. > 2)	0.375 [0.142-0.989]	0.047*	0.052 [0.007-0.403]	0.005*
Smoking status (never smoker vs. former/current smoker)	1.457 [0.735-2.889]	0.281	0.447 [0.052-3.813]	0.461
Histology (adenocarcinoma vs non-adenocarcinoma)	0.941 [0.364-2.431]	0.900	0.109 [0.011-1.103]	0.061
PD-L1(negative vs. positive)	0.821 [0.357-1.888]	0.642	0.410 [0.067-2.508]	0.335
Lines of treatment (< 2 vs. ≥ 2)	0.539 [0.247-1.174]	0.120	0.185 [0.028-1.241]	0.082
T-cirDNA/cirDNA %ratio				
Low (≤ 1%)	-	0.358	-	0.048*
Undetectable	0.675 [0.313-1.457]	0.317	0.102 [0.015-0.718]	0.022*
High (> 1%)	0.522 [0.241-1.261]	0.159	0.133 [0.021-0.849]	0.033*
cirDNA (> 4,5 $ngml^{-1}$ vs. ≤ 4,5 $ngml^{-1}$)	1.094 [0.513-2.332]	0.816	6.623 [1.155-37.977]	0.034*
Treatment (single I/O vs. combined I/O)	2.083 [1.033-4.202]	0.040*	6.359 [1.387-29.149]	0.017*

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