56 HIGH PRETREATMENT DHEA LEVEL IS ASSOCIATED WITH SHORTER OVERALL SURVIVAL IN NEWLY DIAGNOSED METASTATIC NON-SMALL CELL LUNG CANCER PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITORS

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Background Sex is an important factor in determining response to immune checkpoint inhibitors (ICI) in cancer patients.[1] Sex hormones can modulate the immune response in preclinical studies.[2] Our study aimed to determine if the pretreatment sex hormone level can predict outcomes in metastatic non-small cell lung cancer (mNSCLC) patients undergoing ICI therapies.

Methods This study included 61 patients with newly diagnosed mNSCLC who received ICI as part of the upfront therapy. Pretreatment plasma and fecal samples were collected before the first ICI infusion, and we measured sex hormone levels using ultra-high-performance liquid chromatography high-resolution mass spectrometry. Sex hormone levels were compared between the clinical benefit and no clinical benefit group. Patients were then divided into high DHEA and low DHEA groups based on the sex-specific median of the cohort. Overall survival (OS) and progression-free survival (PFS) were compared between high DHEA and low DHEA using Kaplan Meier's methods. A similar analysis was based on the 5-androstenediol level. We used the univariate and multivariate Cox proportional hazards (PH) model to measure hazard ratios (HRs) for PFS and OS.

Results Pretreatment plasma samples were collected from 61 patients, and 31 patients were female (table 1). Among them, 30 plasma samples had measurable DHEA levels, and 46 patients had measurable 5-androstenediol levels (table 2). Patients in the clinical benefit group had significantly higher plasma DHEA levels and 5-androstenediol levels than those in the no clinical benefit group (figure 1)

The high DHEA group had fewer patients with clinical benefits from ICI therapy (27% vs. 87% in the high DHEA and low DHEA groups, respectively) (figure 2). Patients with high DHEA also had shorter OS (mOS: 11.4mo vs. not reached for high DHEA and low DHEA group respectively, p=0.0001) and shorter PFS (mPFS: 4.1mo vs. 22mo for the high DHEA and low DHEA groups, respectively, p<0.0001). High 5-androstenediol also had fewer patients with clinical benefit (46% vs 72% for the high 5-androstenediol and low 5-androstenediol groups, respectively).

Univariate Cox PH analysis confirmed our observation. High DHEA level was associated with poor OS (HR-8.29, 95% CI:2.31–29.79) and PFS (HR=10.23, 95% CI:3.4–30.74). High 5-androstenediol level was associated with shorter PFS (HR=2.26, 95% CI: 1.07–4.75) (table 3).

Conclusions Pretreatment DHEA level and 5-androstenediol level were significantly lower in patients with clinical benefit from ICI. Our study supports the use of pretreatment DHEA as a promising predictive biomarker in patients with metastatic NSCLC receiving ICI therapies.

Ethics Approval This study was approved by Advarra IRB (MCC 18611, PRO00017235).

Abstract 56 Table 1 Patient Demographics and Clinical Characteristics of 61 enrolled patients based on clinic benefit

	clinical benefit N=28	no clinical benefit N=33	P value
age at diagnosis median, range	68[49,84]	67 [52.8, 82.1]	0.89
Male Sex, %	15 (45.5)	15 (53.6)	0.527
Race			0.074
White	31 (94)	23 (82)	
Black	1 (3)	3 (11)	
BMI (median, 95% CI) at the time of treatment	26.1 [18,7, 36.9]	23.8 [16.9,46.9]	0.36
Smoking Status			0.803
Current	9 (32.1)	8 (24.2)	
former	15 (53.6)	21 (63.6)	
never	4 (14.3)	4 (12.1)	
ECOG performance status			0.353
0	5 (15.2)	2 (7.1)	
1	28 (84.8)	25 (89.3)	
histology:			0.529
non-squamous, %	28 (85)	24 (86)	
Squamous, %	5 (15)	4 (14)	
CNS involvement	4 (14.3)	2 (6.1)	0.282
Laboratory Evaluation			
Absolute Neutrophil Count, e3/DL, median, 95% CI	5.1 [2.3, 11.7]	5.1 [3.2,10.5]	0.34
Absolute Lymphocyte Count, e3/DL, median, 95% CI	1.2 [0.3,2.8]	1.05 [0.3, 2.7]	0.61
Absolute Eosinophil Count, e3/DL, median, 95% CI	0.17 [0,0.92]	0.15 [0.01,0.84]	0.32
Absolute Platelet Count, e6/DL, median, 95% CI	262 [109.1, 526.2]	251 [114.4, 469.4]	0.99
Neutrophil to Lymphocyte ratio (median, 95% CI)	4.2 [1.8, 14.8]	4.9 [1.6,13.7]	0.85
Platelet to Lymphocyte ratio (median, 95% CI)	245.6 [62.2, 1104.2]	229.9 [105.7, 796.2]	0.81
Co-morbidities			
COPD	12 (36)	16 (57)	0.11
HLD	22 (66.7)	17 (60.7)	0.63
OSA	6 (18.2)	5 (17.9)	0.97
MI/Heart Failure	3 (9.1)	6 (21.4)	0.18
DM	4 (12.1)	10 (36)	0.038
Prior therapy including neoadjuvant and adjuvant			
Prior chemotherapy	14 (42.9)	20 (61)	0.406
Prior Radiation Therapy	10 (36)	9 (27)	0.478
PD-L1 positive (>1%)	20/27 (74)	14/24 (58)	0.84
if positive, PD-L1 = 50 %, median, 95% CI	9 (32)	10 (30)	0.88
Other mutation			
ALK fusion	1/19	1/20	0.93
EGFR	5/24	2/31	0.16
KRAS	6/19	7/31	0.07
NRAS	0/14	0/15	0.72
TP53	6/11	6/15	0.95

Abstract 56 Table 2 Plasma sex hormone level and stool phytoestrogen level of patients based on clinical benefit

	clinical benefit N=28	No clinical benefit N=33	P value
Plasma			
DHEA level (ng/ml), median, 95% CI	3.7 (2.1-8.3)	9.6 (3.8-16.6)	<0.001
5-androstenediol level (ng/ml), median, 95% CI	2.7 (0.66-5.0)	2.3 (0.87-5.5)	0.01
S-equol level (ng/ml), median, 95% CI	0.11 (0.006-0.32)	0.11 (0.027-3.7)	0.73
Propyl Pyrazole Triol level (ng/ml), median, 95% CI	0.015 (0.0016-0.056)	0.0080 (0.0017-0.079)	0.95
E2 level (ng/ml), median, 95% CI	0.043 (0.013, 0.079)	0.03 (0.009-0.12)	0.43
Stool phytoestrogen level normalized to Daidzein			
Quercetin level, median, 95% CI	0.89 (0.096-129)	0.86 (0.007-15.0)	0.43
Naringenin level, median, 95% CI	1.18 (0.1-48)	0.91 (0.03-29)	0.36
Genestein, median, 95% CI	2.1 (0.07-21)	1.46 (0.07-20)	0.68
S-equol, median, 95% CI	7.81 (0.70-703)	7.38 (0.1-747)	0.58

Abstract 56 Table 3 Univariate and multivariate analysis of clinical factors affecting progress-free survival and overall survival in metastatic non-small cell lung cancer undergoing first line immune checkpoint inhibitor theraphy

Clinical Factors	Progression Free Survival			
	no of events/ no of cases	Univariable-HR (95% CI)	Multivariable HR (95% CI)	no of events/ cases
age	45/61	1.01 (0.98-1.05)	1.11 (1.01,1.23)	34/61
sex				
male	21/30	1	1	17/30
female	24/31	0.85 (0.47,1.53)	1.12 (0.32,3.89)	17/31
p for trend		0.58	0.86	
BMI	45/61	1.00 (0.95,1.06)	1.09 (0.97, 1.22)	34/61
Smoking Status				
current	13/17	1	1	12/17
former	27/36	0.92 (0.47,1.79)	0.25 (0.037, 1.72)	18/36
never	0.625	0.84 (0.30,2.36)	0.20 (0.018, 2.12)	4/8
p for trend		0.94	0.29	
Medical Comorbidities				
DM present	10/14	1.74 (0.85,3.59)	1.14 (0.23,5.68)	10/14
DM absent	35/47	1	1	24/47
p for trend		0.13	0.87	
NLR	45/61	1.01 (0.93,1.09)	1.15 (0.88,1.50)	34/61
PLR	45/61	1.00 (0.99, 1.00)	1.00(0.99, 1.01)	34/61
Systemic therapy within 1 year of immunotherapy Initiation				
yes	23/29	1.12 (0.62, 2.02)	1.39 (0.41, 4.7)	21/29
no	22/32	1	1	13/32
p for trend		0.7	0.59	

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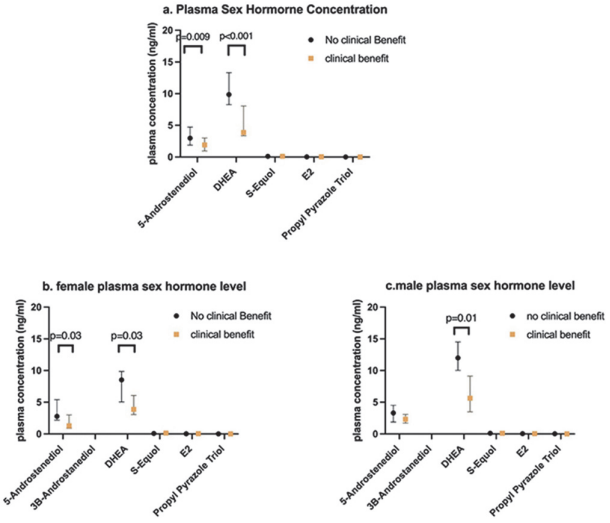
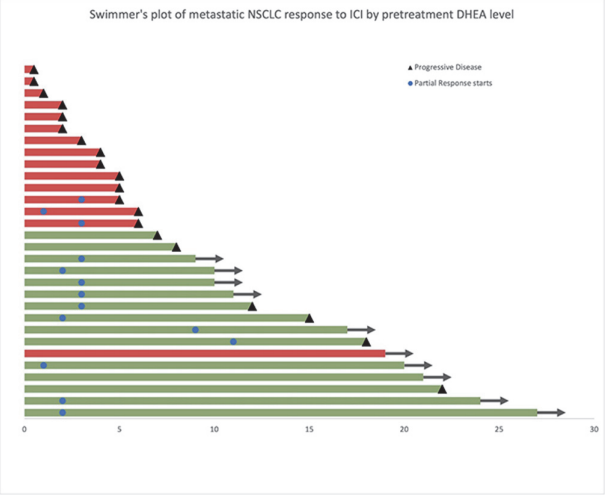


Abstract 56 Figure 1 Plasma sex hormone concentration in clinical benefit and no clinical benefit group. a) all patients b) female only c) male only. The dots/square represents the median and the error bar represented the interquartile changes. The clinical benefit group had significantly lower DHEA and 5-androstenediol plasma concentration



Abstract 56 Figure 2 Swimmer's plot. Patients are color-labeled based on their DHEA level. Patients are arranged based on their duration on therapy. X-axis represented their duration on therapy in months. Red bar represented individual with high DHEA. Green bar represented individual with low DHEA

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