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Blood-Based Biomarker Analysis for Predicting Efficacy of Definitive CCRT and Durvalumab Consolidation in Patients with Unresectable Locally Advanced Non-small Cell Lung Cancer

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Abstract

BACKGROUND: This study aimed to investigate the feasibility of using circulating tumor cells (CTCs) and peripheral blood cells (PBCs) as biomarkers for predicting the efficacy of concurrent chemoradiotherapy (CCRT) and durvalumab consolidation (DC) in patients with locally advanced non-small cell lung cancer (NSCLC).

METHODS: We recruited patients diagnosed with unresectable stage III NSCLC who received definitive CCRT between March 2020 and March 2021. DC was permitted in patients who did not progress after CCRT and tumor PD-L1 ≥1%. Blood samples were collected before (C0) and after CCRT (C1) to calculate PBC counts and analyze CTCs. CTCs, isolated using CD-PRIME^{TM} system, exhibited EpCAM/CK+/CD45− phenotype in BioViewCCBS^{TM}.

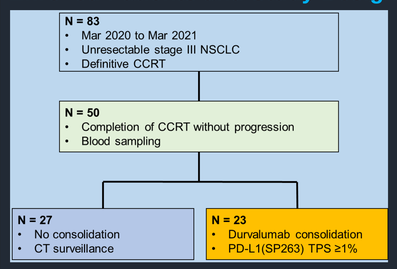
RESULTS: A total of 50 patients were enrolled and 23 patients received DC. The median progression-free survival (PFS) was not significantly different between patients with and without DC (13.1 vs. 13.5 months; p=0.355). In overall, patients with higher platelets (PLT^{hi}, >252 x 103/uL) at C1 had worse median PFS than those with lower platelets (PLT^{lo}, ≤252 x 103/uL) (5.9 vs. 15.1 months; p<0.001). In DC group, patients with residual CTC clusters after CCRT (C1) had worse median PFS than those without detectable CTC cluster (9.5 months vs. not reached; p=0.034). In multivariate analysis, PLT^{hi} at C1 was an independent factor for PFS (hazard ratio [HR] 4.12, 95% confidence interval [CI] 1.77-9.61; p=0.001), and patients with DC who had PLT^{hi} and residual CTC clusters at C1 showed the worst PFS (2.6 months, HR 44.40; p=0.001), even worse than those without DC who had PLT^{hi} (5.9 months, HR 15.65; p=0.002).

CONCLUSION: Comprehensive analysis of CTC and PBC counts before and after CCRT, especially CTC clusters and platelets at C1, demonstrated they might be biomarkers for predicting survival. This finding could aid in risk stratification of patients with unresectable stage III NSCLC who are eligible for DC after definitive CCRT.

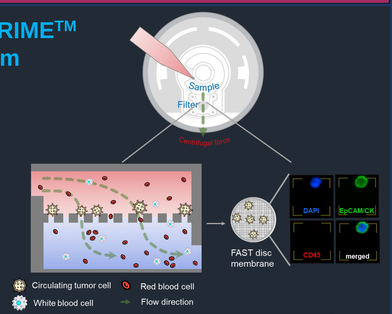
Keywords: circulating tumor cells; platelets, biomarkers; concurrent chemoradiotherapy; durvalumab; non-small cell lung cancer

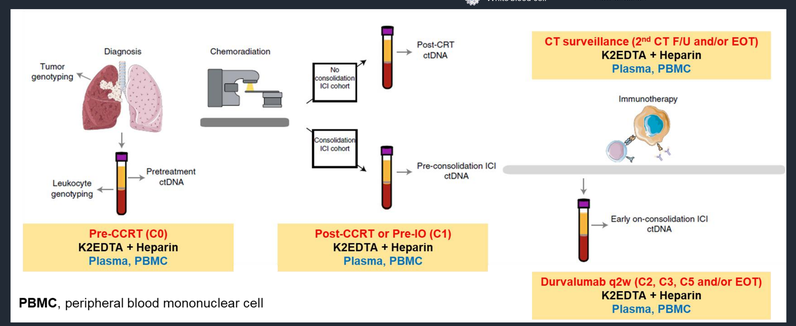
Study subjects & Methods

Enrolled Patients and Study Design



CD-PRIME^{TM} system





PBMC, peripheral blood mononuclear cell

Results

Baseline Characteristics

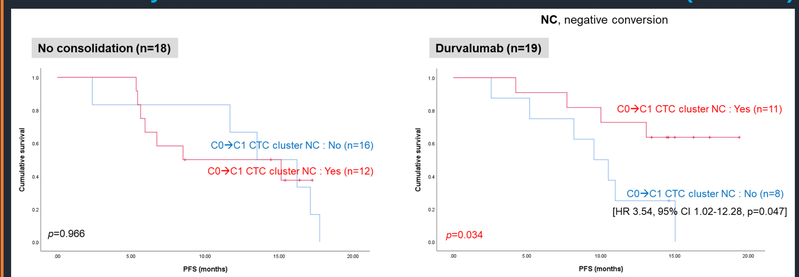
Variables, n (%)	CCRT (n=50)	No consolidation (n=27)	Durvalumab (n=23)	P-value
Age, median (range)	70 (49-81)	70 (53-78)	69 (49-81)	0.740
Sex : Female / Male	4 (8) / 46 (92)	1 (4) / 26 (96)	3 (13) / 20 (87)	0.322
Smoking : Never / Current / Ex	3 (6) / 28 (56) / 19 (38)	2 (7) / 15 (56) / 10 (37)	1 (4) / 13 (57) / 9 (39)	0.900
Never / Ever	3 (6) / 47 (94)	2 (7) / 25 (93)	1 (4) / 22 (96)	1.000
Pack-years, median (range)	40.0 (0.0-100.0)	40.0 (0.0-90.0)	40.0 (0.0-100.0)	0.239
Comorbidity : No / Yes	8 (16) / 42 (84)	6 (22) / 21 (78)	2 (9) / 21 (91)	0.261
Charlson index, median (range)	5 (2-10)	5 (3-10)	5 (2-8)	0.984
Histology : ADC / SQC / NSCLC,NOS	16 (32) / 30 (60) / 4 (8)	10 (37) / 14 (52) / 3 (11)	6 (26) / 16 (70) / 1 (4)	0.402
Non-squamous / Squamous	16 (35) / 30 (65)	10 (42) / 14 (58)	6 (27) / 16 (73)	0.306
Stage : IIIA / IIIB / IIIC	23 (46) / 19 (38) / 8 (16)	12 (44) / 11 (41) / 4 (15)	11 (48) / 8 (35) / 4 (17)	0.906
EGFR mutation : L858R / Wild / NA	1 (2) / 22 (44) / 27 (54)	1 (4) / 14 (52) / 12 (44)	0 (0) / 8 (35) / 15 (65)	0.264
ALK translocation : Positive / Negative / NA	2 (4) / 20 (40) / 28 (56)	1 (4) / 13 (48) / 13 (48)	1 (4) / 7 (31) / 15 (65)	0.442
PD-L1 IHC (TPS)				
SP263 (n=49) : ≥1% / <1%	28 (57) / 21 (43)	6 (23) / 20 (77)	22 (96) / 1 (4)	0.000
SP263 (n=49) : ≥50% / <50%	9 (18) / 40 (82)	3 (12) / 23 (88)	6 (26) / 17 (74)	0.273

Variables	CCRT (n=50)	No consolidation (n=27)	Durvalumab (n=23)	P-value
CCRT				
Chemotherapy regimen : TP / TC	34 (68) / 16 (32)	18 (67) / 9 (33)	16 (70) / 7 (30)	0.827
Chemotherapy cycle, median (range)	6 (1-6)	6 (1-6)	6 (5-6)	0.035
RT fraction, median (range)	30 (4-30)	30 (4-30)	30 (30-30)	0.032
RT dose, Gy, median (range)	60.0 (8.0-75.0)	60.0 (8.0-75.0)	60.0 (56.5-60.0)	0.711
RT duration, days, median (range)	42 (6-57)	41 (6-57)	42 (39-48)	0.014
Duration btw last RT and IO, days (n=23), median (range)	-	-	28 (9-42)	-
Duration btw last RT and C1 sample, days (n=48), median (range)	31.5 (1-69)	42 (1-69)	28 (9-42)	0.001
Durvalumab consolidation			23	
On going Durvalumab / 1-Year completion	-	-	1 (4) / 10 (43)	-
Progression / Progression on treatment	-	-	13 (57) / 12 (52)	
Discontinuation due to AE (IO, not PD)[a]	-	-	3 (13)	
Progression	31 (62)	18 (67)	13 (57)	0.461
Locoregional	15 (48)	10 (56)	5 (39)	0.521
Locoregional + Systemic	3 (10)	1 (6)	2 (15)	
Systemic	13 (42)	7 (39)	6 (46)	
Post-progression treatment				-
Chemotherapy / TKI / IO / Re-RT	13 (26) / 3 (6) / 3 (6) / 3 (6)	3 (11) / 2 (7) / 3 (11) / 2 (7)	10 (43) / 1 (4) / 0 (0) / 1 (4)	
BSC / FU loss	2 (4) / 3 (6)	2 (7) / 3 (11)	0 (0) / 0 (0)	

Treatment Efficacy

Variables, n (%)	CCRT (n=50)	No consolidation (n=27)	Durvalumab (n=23)	P value
CCRT – Best response				
PR / SD / PD	33 (66) / 14 (28) / 3 (6)	16 (59) / 8 (30) / 3 (11)	17 (74) / 6 (26) / 0 (0)	0.221
ORR (CR+PR)	33 (66)	16 (59)	17 (74)	0.276
DCR (CR+PR+SD)	47 (94)	24 (89)	23 (100)	0.240
Durvalumab – Best response				
PR / SD / PD / NE	-	-	0 (0) / 19 (82) / 2 (9) / 2 (9)	-
ORR (CR+PR)	-	-	0 (0)	-
DCR (CR+PR+SD)	-	-	19 (82)	-
Follow-up duration, months, median (95% CI)	16.3 (15.4-17.3) (cf. PACIFIC in 2017 NEJM – 14.5 months)	16.4 (14.6-18.2)	16.3 (14.3-18.3)	0.166
PFS, months, median (95% CI)	13.1 (8.5-17.6)	13.5 (5.4-21.6)	13.1 (8.5-17.6)	0.355
OS, months, median (95% CI)	NR	NR	NR	0.060
Adverse events				
Radiation pneumonitis	40 (80)	21 (78)	19 (83)	0.736
On steroid treatment	10 (25)	4 (19)	6 (32)	0.473
Radiation esophagitis	24 (48)	13 (48)	11 (48)	0.982
Immune-related AE[a]	-	-	13 (54)	-
Discontinuation due to irAE[b]	-	-	3 (13)	-

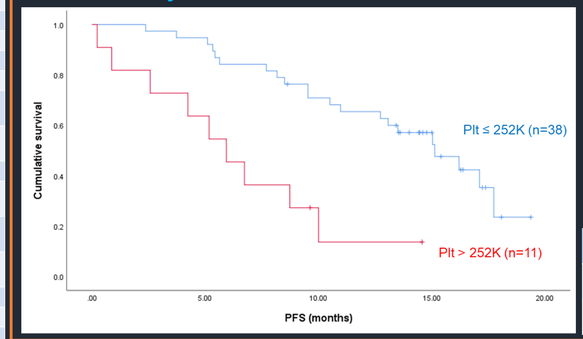
Survival analysis – PFS : CTC clusters before and after CCRT (C0 → C1)



	Median PFS, mons (95% CI)	P-value
C0→C1 CTC cluster NC : Yes	8.5 (0.0-19.9)	0.966
C0→C1 CTC cluster NC : No	13.5 (8.1-18.9)	

	Median PFS, mons (95% CI)	P-value
C0→C1 CTC cluster NC : Yes	NR	0.034
C0→C1 CTC cluster NC : No	9.5 (6.3-12.8)	

Survival analysis – PFS : Platelet count after CCRT (C1)



	Median PFS, mons (95% CI)	P-value
C1 Plt ≤ 252K (n=38)	15.1 (11.9-18.4)	0.000
C1 Plt > 252K (n=11)	5.9 (3.2-8.6)	

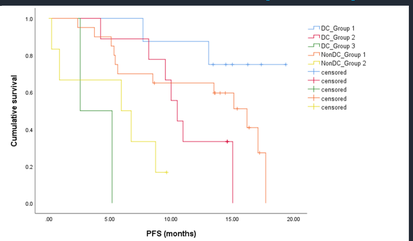
Survival analysis – PFS : CTC clusters and Platelet count (C0→C1)

Durvalumab consolidation (n=19)

Group 1 : C1 PLT ≤ 252K and C0→C1 CTC cluster undetectable
Group 2 : If one variable is the opposite
Group 3 : C1 PLT > 252K and C0→C1 CTC cluster residual

No consolidation (n=26)

Group 1 : C1 PLT ≤ 252K
Group 2 : C1 PLT > 252K



DC, durvalumab consolidation

		Median PFS, mons (95% CI)	P-value	Adjusted HR (95% CI)	P-value
	DC_Group 1 (n=8)	NR	0.000	Ref = 1.0	0.002
	DC_Group 2 (n=9)	10.5 (9.0-12.0)		6.22 (1.22-31.67)	0.028
⇨	DC_Group 3 (n=2)	2.6		44.40 (5.13-384.51)	0.001
	NonDC_Group 1 (n=20)	16.2 (12.4-20.0)		3.30 (0.74-14.83)	0.119
⇨	NonDC_Group 2 (n=6)	5.9 (0.0-13.0)		15.65 (2.73-89.54)	0.002

[a]Thyroiditis(9), Skin eruption(2), DILD(1), Fever(1), Pericardial effusion(1), Sudden-onset sensorineural hearing loss(1).

[b]DILD(1), Fever(1), Pericardial effusion(1).