Chromosomal instability (CIN) biomarker in circulating tumor cells (CTC) may predict for therapy resistance in metastatic castration-resistant prostate cancer (mCRPC)

Niamh M Keegan[1], Joseph D. Schonhoft[2], Ethan S. Barnett[1], Erica Dayan[1], Jimmy L. Zhao[1,3], Emily A. Carbone[1] , Michelle Zanone[1], Amanda Anderson[2] , Rick Wenstrup[2], Howard I. Scher[1,4]

1) Genitourinary Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA. 2) Epic Sciences, San Diego, California, USA. 3) Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New, York, New York, USA. 4) Department of Medicine, Weill Cornell Medical College, New York, New York, USA

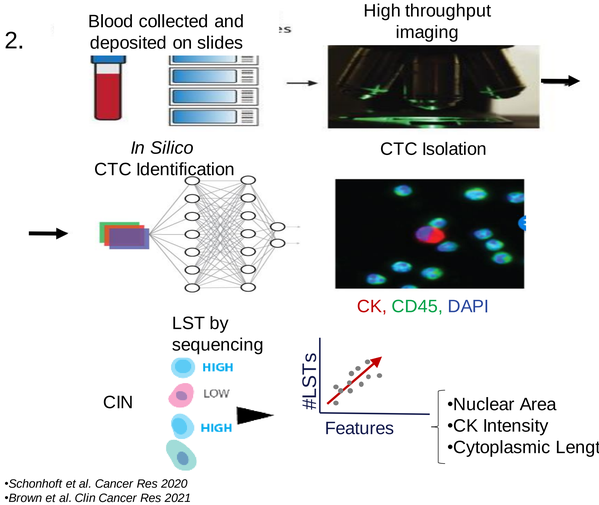
BACKGROUND: Large scale transitions (LSTs) are chromosomal breakages that generate gains or losses ≥10 Mb. As an indicator of CIN, we previously validated a single-cell phenotypic classifier for identification of CTCs with at least 9 LSTs per cell (pLST-high). High CIN, defined as 3 or more pLST-high CTCs at baseline, was associated with shorter overall survival. Here, we explored high CIN as a predictive marker of drug sensitivity for patients (pts) with mCRPC.

STUDY DESIGN

Retrospective analysis of 212 pre-treatment blood samples from 179 unique patients with progressing mCRPC

1. CTC samples were collected prior to taxane based chemotherapy or an androgen receptor signaling inhibitor (ARSi).

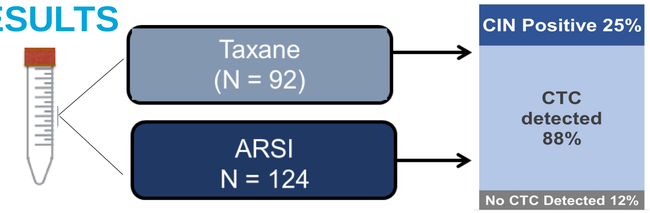
2.



•Schonhoft et al. Cancer Res 2020
•Brown et al. Clin Cancer Res 2021

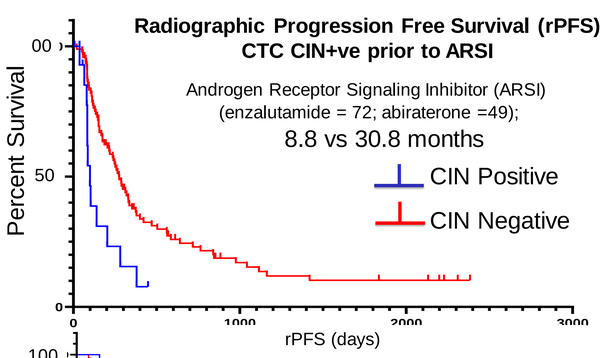
3.. Radiographic progression was defined as new or increasing lesions on treatment per retrospectively reviewed clinical radiology reports.

RESULTS



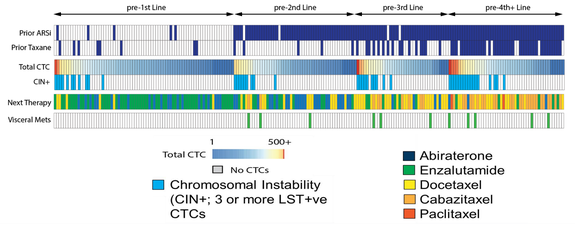
Patient demographics

	ARSI (N=124)	Taxane (N=92)	Overall (N=216)
Age (years), median (min, max)	67 (45-90)	68 (48-90)	67 (45-87)
Line of Therapy			
1	70 (56.5%)	6 (6.5%)	76 (35.2%)
2	35 (28.2%)	17 (18.5%)	52 (24.1%)
3	10 (8.1%)	29 (31.5%)	39 (18.1%)
3+	9 (7.3%)	40 (43.5%)	49 (22.7%)
Prior ARSI			
No	70 (56.5%)	5 (5.4%)	75 (34.7%)
Yes	54 (43.5%)	87 (94.6%)	141 (65.3%)
Prior Taxane			
No	100 (80.6%)	46 (50.0%)	146 (67.6%)
Yes	24 (19.4%)	46 (50.0%)	70 (32.4%)
Lab Values; median (min, max)			
PSA ng/mL	20.0 (0.0900, 1550)	117 (0.0600, 16300)	37.5 (0.0600, 16300)
LDH U/L	209 (123, 1290)	248 (141, 1000)	222 (123, 1290)
ALK U/L	93.0 (47.0, 2170)	128 (43.0, 1820)	104 (43.0, 2170)
HgB g/dL	12.8 (7.20, 15.1)	11.6 (8.20, 14.3)	12.2 (7.20, 15.1)
Visceral Mets			
No	111 (89.5%)	62 (67.4%)	173 (80.1%)
Yes	11 (8.9%)	21 (22.8%)	32 (14.8%)
Missing	2 (1.6%)	9 (9.8%)	11 (5.1%)



Endpoints	ARSI	Taxane
Time on Drug; Median (Min, Max)	6.08 (0.132, 71.4)	3.49 (0.493, 23.9)
rPFS Months; Median (Min, Max)	5.97 (0, 79.2)	4.18 (0, 12.1)
rPFS Event	88 (71.0%)	76 (82.6%)
OS Months; Median (Min, Max)	24.9 (0.756, 81.5)	12.7 (2.37, 65.9)
Death Events	105 (84.7%)	89 (96.7%)

CIN positivity is more frequent post taxane and post ARSI therapy



CIN Biomarker positivity remains significantly associated with shorter rPFS and OS in multivariate modeling adjusting for known prognostic factors

Covariates	rPFS HR (95% CI)	P
CIN Status, Positive vs. Negative)	2.32 (1.16 - 4.66)	0.0176
Next therapy, Taxane vs. ARSi	1.43 (0.91 - 2.26)	0.1245
Therapy Line, pre-1st vs 2nd or greater	0.29 (0.19 - 0.47)	<0.0001
LDH IU/L, ≥ 250 vs < 250	1.15 (0.74 - 1.77)	0.5342
Alkaline Phosphatase IU/L, ≥140 vs <140	0.97 (0.64 - 1.46)	0.8685
PSA ng/mL , ≥ 20 vs < 20	1.06 (0.71 - 1.59)	0.7614
Hemoglobin g/dL, < 12 vs ≥ 12	1.40 (0.92 - 2.11)	0.112
Presence of Visceral Metastases, Yes vs No	1.34 (0.85 - 2.13)	0.2121
Interaction CIN Status : Next Therapy	0.47 (0.20 - 1.09)	0.0766

Covariates	OS HR (95% CI)	P
CIN Status, Positive vs. Negative)	5.28 (2.82 - 9.89)	<0.0001
Next therapy, Taxane vs. ARSi	1.53 (1.01 - 2.30)	0.0444
Therapy Line, pre-1st vs -2nd or greater	0.40 (0.27 - 0.59)	<0.0001
LDH IU/L, ≥ 250 vs < 250	1.40 (0.98 - 2.00)	0.0606
Alkaline Phosphatase IU/L, ≥140vs< 140	0.94 (0.66 - 1.34)	0.7451
PSA ng/mL , ≥ 20 vs < 20	1.30 (0.92 - 1.86)	0.1388
Hemoglobin g/dL, < 12 vs ≥ 12	1.77 (1.22 - 2.55)	0.0024
Presence of Visceral Metastases	1.25 (0.82 - 1.91)	0.2976
Interaction CIN Status : Next Therapy	0.26 (0.12 - 0.56)	0.0006

CONCLUSIONS: In this study, CIN positivity was predictive for shorter rPFS and OS. CTC CIN positivity predicted for a poorer response to ARSi therapy in contrast to a taxane, the response to which was independent of CTC CIN status. This warrants further prospective validation.