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Retrospective Review of 374 Samples, Circulating DNA; as a Biomarker Assay to Support Clinical Management in Solid Tumors Treated With Multi Targeted Epigenetic Therapy (MTET)

M A Nezami

President and CEO, Sahel Oncology LLC, USA

ABSTRACT

Here in this abstract we retrospectively review preliminary findings on 374 samples of circulating DNAextracted from 173 patients treated by multitargeted epigenetic therapy (MTET), which is a combination of natural histone deacetylase inhibitors and DNMT methyl transferase inhibitors. This therapy could dynamically interrupt the expression of altered genes, in a variety of solid tumor types, both in invitro and invivo models. We hypothesize that serial monitoring of the circulating DNA provides a feasible option for therapeutic decisions making based on presence of the driver genes in these cases. We also were able to track the antineoplastic response in these group of patients by monitoring their tumor circulating DNA mutated allele fractions and propose a direct correlation with interim epigenetic therapy effectiveness.

***Corresponding author**

M.A. Nezami MD, President and CEO, Sahel Oncology LLC, Orange Coast Medical Center of Hope Inc. 496 Old Newport Blvd. #7, Newport Beach, CA 92612, Tel: (949) 515 4673(HOPE); E-mail: amnezami@yahoo.com

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Introduction

Our current understanding of cancer biology, and the epigenetic science has transformed our ability to deliver therapies more precisely to the genetic and epigenetic targets driving the tumor growth and disrupting it's behavior. In concert with our efforts to regulate the transcription of altered genes involved in tumor biology, we have emphasized a range of epigenetically regulated driver genes that control the tumor key molecular targets, involved with it's growth and metastasis [1]. Statistical analysis on epigenetically driven targets had shown improved outcome compared to historical control [2].

Unfortunately epigenetic targets are dynamically expressed and no single drug can clinically be used to target the epigenome as drugs have static mechanism of action [3]. This limiting factor has caused researchers in the field to admit their failure in development of an epigenetic formula or product that has significant clinical impact in majority of cancer types, mainly solid tumors. As a result, the efforts on epigenetic drug development has shifted in recent years to hematological cancers, such as lymphomas and leukemias where these drugs can make a difference in the clinic [4-13].

We earlier had shown that a combination of histone and DNA selective demethylators used in a specific protocol, was able to significantly produce meaningful results in our experimental therapeutic models. Although cytotoxic therapies, and targeted drugs have been studied in the recent years to correlate with such relevance, using liquid biopsy in different types of cancer, including lung, lymphoma, renal cancer, breast cancer, colon cancer, ovarian cancer, this is to our knowledge the first time this correlation with epigenetic drugs have been explored [14-28].

Method and materials

173 cases treated by MTET were collectively selected without selection bias. These cases were treated all in associated clinics of Medical centers of Hope.

The biomarker assays were performed through liquid biopsy through 374 samples. Amongst them 300 samples were positive for circulating DNA. 74 were negative. 66 patients had one sample and 63 patients had at least two samples (Table 1).

Dr. Nezami G360 data

	Number of tests	Number of patients
374 samples sent through the end of May 2018 on 173 patients. More than 1/2 patients in the practice (61%) have had serial testing (2 or more G360 tests).	1	66
	2	63
	3	17
	4	13
	5	9
	6	2
	7	2
	8	1
	total	173

Other and misc. categories	Other/MISC	Count of cancertype
	Anal Squamous Cell Carcinoma	2
	Anaplastic Thyroid Carcinoma	1
	Cencer, Other	2
	Carcinoma of Unknown Primary (CUP)	7
	Glioblastoma	3
	Glioma	1
	Neuroendocrine Carcinoma	1
	Other	17
	Squamous Cell Carcinoma	1
	Thyroid Carcinoma	4
	Grand Toatl	**42**

Detection rate was 86 percent. The most and least common tumor types: 134 cases had breast cancer. 4 had glioblastoma. 20 cases carried BRCA alterations. In average 64 percent of such cases were stage four and had no other viable options left.

Results

Serial monitoring of mutated allele fraction in circulating DNA analysis is feasible and clinically meaningful, when epigenetic drugs are applied in clinic and show positive clinical outcome based on such biomarker driven approach to epigenetic targets.

Further analysis as of April of 2019, for 491 cases is currently on going and preliminary findings are consistent with this article with common genetic mutations reflected in breast cancer responding to the epigenetic therapies (Tables 2 & 3).

Dr. Nezami G360 data		
	Cancer Category	**Count of samples**
Samples to date by cancer type, through end of April, 2019	BLADDER	7
	BONE/ SOFT TISSUE	14
	BREAST	186
	CERVIX	5
	ENDOMETRIAL/ Uterine	11
	GI	59
	HEAD NECK	16
	KIDNEY	7
	LUNG	34
	PROSTATE	50
	Misc/Other*	42
	OVARIAN	34
	SKIN	26
	Grand Total	491

Dr. Nezami G360 data		
	Cancer Category	**Count of samples**
common gene mutations breast cancer samples (genes identified 10 or more times in breast cancer samples to date)	Grand Total	644
	PIK3CA	61
	TPS3	44
	ERBB2	36
	ESR1	32
	NF1	32
	EGFR	27
	ARID1A	26
	KIT	23
	MYC	22
	CCND1	21
	BRCA1	20
	BRCA2	20
	FGFR1	20
	MET	20
	APC	18
	RAF1	16
	FGFR2	15
	PDGFRA	14
	BRAF	12
	GATA3	12
	CCNE1	11
	CDK6	10
	NOTCH1	10

ERBB2	36
CNV	14
SNV	22

4/22 SNVs: activating

We conclude that such biomarker based target identification and selective epigenetic approach in cancer therapy could replace the current standard of care which is mainly blind shot and type specific.

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