

# A Retrospective Review of 300 Case Reports, Quality of Life and Correlation with Biomarkers Related To Tumor Burden, in Advanced Cancer

Amin M Nezami\*

Sahel Oncology LLC, Orange Coast Medical Center of Hope Inc., 496 Old Newport Blvd. #7, Newport Beach, CA 92612, USA

## ABSTRACT

It is currently the tumor size measured by Response Evaluation Criteria in Solid Tumors (RECIST) criteria that is considered an indication for objective response to any effective therapy in cancer, however in advanced solid tumors, this indicator has been debated recently as it fails to correlate with clinical response, quality of life and even overall survival. In this short but large sample size case review, we look into a meaningful potential substitute for such metrics, defined by surrogates of tumor burden, and correlate that with biomarkers that can be easily measured through blood sample, such as tumor circulating DNA (ctDNA). We suggest further studies to be considered to validate our findings and propose a shift in current clinical practice by further generation of hypothesis, based on our review.

## BACKGROUND

Unresectable metastatic solid tumors is, with rare exception, a fatal disease eventually. A few patients may enter a prolonged remission. However, for the majority of patients with metastatic disease, chemotherapy is administered with palliative intent to decrease tumor bulk, and prolong survival. That said the specific endpoints that best reflect benefit from systemic chemotherapy in metastatic disease remain unclear.

Objective response rates, as judged by a decrease in the size of measurable lesions, are increasingly considered to be poor surrogates for benefit in this family of cancers. The "disconnect" between objective tumor response and quality of life is particularly evident in studies of drugs such as molecularly targeted therapies.

Increasing attention is being paid to other important indicators of clinical outcomes, such as reduced tumor burden, improved quality of life and disease stabilization. Stabilization of disease is increasingly viewed as a realistic endpoint for metastatic disease [1-3]. Studies monitoring patients during treatment have shown that lower ctDNA dynamics correlate with better treatment response in colorectal ovarian, breast, non-small cell lung cancer (NSCLC), and melanoma [4-9].

## METHODS

We randomly selected and reviewed 300 cases treated solely or with

an integration of supportive care with standard therapies through natural epigenetic therapy, aiming at reducing the metastatic tumor burden, measured by quality of life indicators as well as surrogate biomarkers such as circulating DNA, and circulating tumor cells. All patients started the program after educating them about their possible options of conventional and nonconventional treatments and consents obtained. The progression of disease was measured during or after the course of treatment through Tumor markers, growth factors, Imaging studies and markers for cancer growth, necrosis, LDH, circulating DNA and Circulatory tumor cells (CTC). In this review particularly the circulating DNA was randomly selected as biomarkers of tumor burden. The Table 1, manifests the most common findings in breast cancer cases, as an example. Table 2 manifests the cancer type category of the samples examined on April 2019.

Treatment consisted of multitargeted epigenetic therapy (MTET) in a patented protocol which consists intravenous application of off label natural histone deacetylase inhibitors and demethylators.

Patients were 21 to 83 years old, with mixed ethnicities and backgrounds. More than  $\frac{3}{4}$  of the patients had received and exhausted prior traditional care. The minimum treatment course was two weeks and patients data were followed up to 10 years post therapy, when available (2010-2020).

Results: There were statistically significant positive changes

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

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Gene	Observed in data
<b>Grand Total</b>	<b>644</b>
<b>PIK3CA</b>	61
TP53	44
<b>ERBB2</b>	36
<b>ESR1</b>	32
NF1	32
EGFR	27
ARID1A	26
KIT	23
MYC	22
CCND1	21
<b>BRCA1</b>	20
<b>BRCA2</b>	20
FGFR1	20
MET	20
APC	18
RAF1	16
FGFR2	15
PDGFRA	14
BRAF	12
GATA3	12
CCNE1	11
CDK6	10
NOTCH1	10

Common gene mutations breast cancer samples (genes identified 10 or more times in breast cancer samples to date).

Table 1: Common findings in breast cancer cases.

Cancer Category	Count of samples
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
<b>Grand Total</b>	<b>491</b>

Samples to date by cancer type, through end of April, 2019

\*Definitions on following slide

Table 2: Cancer type category of the samples examined.

in performance scales of patients with advanced disease by integration of the palliative and supportive care. In the first two weeks post initiation of the therapy, there was in average 1.3 point improvement in ECOG scoring. We also observed reduced hospitalizations and associated morbidities compared to historical data, as control. This finding was associated with a positive desirable change in biomarkers, defined by liquid biopsy. The circulating tumor cell analysis confirmed 85 percent reduction of mRNA expressions of all EpCAM markers, indicated by the lab (Biofocus Lab) Telomerase, ERBB2, c Myc, and CK 19/20. This reduction was noticed in average after 10 treatments.

**CONCLUSIONS**

We conclude that objective antitumor response defined by tumor size, may not necessarily reflect the best end point for clinical response. As such successful therapeutics could still improve clinical outcome by reducing tumor metastatic burden, measured by surrogates such as circulating DNA, and improving quality of life. We suggest that further studies be conducted to prove the concept and development of novel epigenetic therapies aimed at reducing metastatic burden and quality of life in advanced solid

tumors, and further integrated in the therapeutic approach to patients with advanced disease.

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