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# Onco News

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## *From the Desk of Editor*

### Liquid Biopsies :Will it replace formal biopsy ?

Dear Readers

Happy Deewali and festive season .

As the concept of precision medicine in the field of cancer management continues to evolve, so do the challenges and demands with regards to diagnosis, prognosis and prediction of treatment resistance. Although the discovery of molecular agents able to target specific genomic changes in metastatic cancer patients has revolutionized patient care, tumor heterogeneity remains a daunting obstacle for clinicians who need to optimize therapy regimens based on an individual's cancer genome. Tissue biopsies, which still currently represent the standard of tumor diagnosis, unfortunately only reflect a single point in time of a single site of the tumor. Such a sampling method is thus inadequate for the comprehensive characterization of a patient's tumor, as it has been demonstrated that various areas within the primary tumor or metastases can in fact harbor different genomic profiles. The molecular genetic diversity within a tumor can also alter over time, thus rendering future treatment decisions based on historical biopsy information potentially inaccurate and suboptimal. Furthermore, a surgical biopsy procedure is hampered by limited repeatability, patient age and co morbidities, costs and time potentially leading to clinical complications. The advent of next-generation sequencing (NGS) technologies has proven its value in the search for novel, more comprehensive and less invasive biomarkers in order to truly realize the goals of cancer precision medicine.

Such minimally invasive tests, know as a “Liquid biopsies” or Blood biopsy have gained plenty of attractions in the last few years.

With regards,
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M.D., D.M.
Senior Medical Oncologist

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**Introduction:**

In this issue I briefly summarize the current technologies and applications, the detection rates and the new technologies and emerging concepts as well as existing challenges for liquid biopsy applications.

Current technologies and applications: Liquid biopsy can be done broadly by :

A. Circulating tumor DNA (ct DNA)
B. Circulating tumor cells (CTCs)
C. Exosomes
D. Epigenetics: plasma bisulfate sequencing and nucleosome mapping

**A. Circulating tumor DNA (ct DNA):**

Technologies based on the analysis of ctDNA can be mainly classified as targeted or untargeted. Targeted

approaches are used to analyze single nucleotide mutations or structural chromosomal rearrangements in specified genomic regions of plasma DNA and to estimate the allelic frequency of a particular mutation within a sample.It can be performed by quantitative or digital PCR. Using digital PCR, ctDNA could be detected in >75% of patients with advanced cancers and in 48-73% of patients with localized tumors. These technologies require prior knowledge of the region of interest to detect known mutations . As these genomic rearrangements are not present in normal human plasma or tissues unrelated to the tumor, their detection has a high specificity and sensitivity.

In contrast untargeted approaches do not depend on a priori knowledge and aim at a comprehensive analysis of the tumor genome. Whole-genome sequencing of plasma DNA allows the comprehensive characterization of structural variations and somatic copy number alteration (SCNAs). These assays have similarities to "digital karyotyping".

**B. Circulating tumor cells (CTCs) :**

A second approach to liquid biopsy examines whole tumor cells in the bloodstream, known as CTCs.

A strength of CTC analysis is that, as a single-cell approach, not only pure tumor DNA but also pure tumor RNA can be obtained.

**C. Exosomes :**

A third target of liquid biopsies involves exosome, which are circulating vesicles harboring nucleic acids shed by living cells as well as tumors. Exosomes can range from 30 to 200 nm in size and can be isolated from plasma, saliva, urine, and cerebrospinal fluid as well as from serum. Since they are stable carriers of DNA, RNA, and protein form the cell origin, this makes them particularly attractive as biomarkers of cancer. Moreover, exosomes can harbor RNA with tumor-specific mutations and DNA originating from these vesicles can be used to detect both gene amplifications and mutations.

Importantly, exosomes may have the potential to detect very early cancer stages, as recently shown in patients with pancreatic cancer. These exosomes allowed the reliable detection of pancreatic intraepithelial lesions at very early stages despite negative signals by magnetic resonance imaging, which may enable curative surgical interventions in this otherwise dismal disease.

**Mutation baseline value in healthy individuals:**

A great promise attributed to liquid biopsies is their possible potential to detect cancer early or even to detect precursor lesion before clinical signs occur or before sophisticated imaging systems are able to detect them. It is possible for healthy individuals to harbor disadvantageous variants without exhibiting any apparent disease phenotype. Cancer-associated mutations might be identified in plasma DNA from healthy persons.

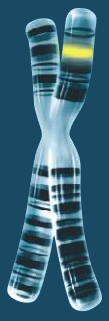
**D. Epigenetics: plasma bisulfate sequencing and nucleosome mapping**

Of special interest are studies of cfDNA methylation patterns, since plasma contains a mixture of DNA from different tissues and organs. Indeed, such a procedure may achieve sensitivities suitable not only for cancer detection but also for other clinical conditions such as type I diabetes, multiple sclerosis, acute brain damage following cardiac arrest, or traumatic brain injury.

**Challenges for liquid biopsy applications and how close are we to the clinic :**

For patients with NSCLC the implementation of cfDNA in EGFR mutation analysis severs as first blood-based companion diagnostic to test which patients are potential candidates for the drug Gefitinib or Afatinib. Patients treated with first-line EGFR tyrosine kinase inhibitor had acquired the EGFR T790M mutation, which confers resistance to first-generation EGFR tyrosine kinase inhibitors. NSCLC patients with this T790M mutation who were treated with osimertinib had better response rates and progression-free survival than patients treated with platinum based chemotherapy. This is a beautiful example in which an invasive lung tissue biopsy was replaced by a plasma DNA-based blood test, i.e. a liquid biopsy, to identify a group of patients who could benefit from a specific treatment. This will likely propel development of future NGS-based EGFR mutation detection assays, which are of particular relevance for the Asian population in which EGFR mutation-positive lung cancers occur more frequently than in the Caucasian population.

However, before liquid biopsies can serve as viable diagnostic assays, pre-analytical steps, such as the collection of biofluid (e.g. blood, serum, plasma), centrifugation settings, isolation reagents and storage conditions, must be standardized in order to ensure reproducible processing procedures.



# CRIZALK™ – first choice, first-line[1]

## First-line CRIZALK™ increased median PFS by > 90% compared with chemotherapy in Asian Patients[1,2]

**Median PFS[2]**
**(Asian Patients)**

| CRIZALK™ | Chemotherapy |
|---|---|
| 13.6 months | 7.0 months |

P<0.001

**RAPID MEDIAN RESPONSE TIME[1]**

| CRIZALK™ | Chemotherapy |
|---|---|
| 1.4 months | 2.8 months |

- CRIZALK™ extended intracranial TTP compared with chemotherapy[3]
- CRIZALK™ has a well-established, generally tolerable and manageable side-effect profile[1]
- For patients living with advanced ALK-positive NSCLC, CRIZALK™ offers an improved quality of life compared with chemotherapy[1]

Crizotinib is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an IHC/FISH test [4]

ALK- anaplastic lymphoma kinase; DCR-disease control rate; FDA-Food and Drug Administration; NSCLC-non-sm all-cell lung cancer; ORR-objective response rate; PFS-progression-free survival; TTP - time to tumour progression.

References: 1. Solomon B, et al. N Engl J Med 2014;371:2167–77.
2. Mok T, et al. Abstract 0-26 Presented at the 55th Annual Meeting of JLCS 2014, Kyoto, Japan, Nov 14-16, 2014
3. Solomon B, et al. Presented at European Society of Medical Oncology Congress, 28 September 2014, Barcelona, Spain: Abstract 12250.
4. Crizotinib, Local Prescribing Document, Pfizer India. LPD Version 5 LPDCR1072014.

**SUMMARY OF PRESCRIBING INFORMATION FOR CRIZOTINIB (Based on LPD version 7.0 LPDCRI052016)**

**Composition:** Each capsule contains either 250 mg or 200 mg of Crizotinib. Indications: Crizotinib is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an IHC/FISH test. Contraindications: Use of crizotinib is contraindicated in patients with hypersensitivity to crizotinib or to any of the excipients. Severe hepatic impairment.**Adverse reactions:** The most common adverse reactions (≥ 25%) in patients with ALK-positive NSCLC are vision disorder, nausea, diarrhoea, vomiting, oedema, constipation, elevated transaminases, decreased appetite, fatigue, dizziness, and neuropathy. The most serious adverse reactions in patients with ALK-positive advanced NSCLC are hepatotoxicity, ILD/pneumonitis, neutropenia and QT interval prolongation. The most frequent adverse reactions (≥3%, all-causality frequency) associated with dosing interruptions were neutropenia (11%), elevated transaminases (7%), vomiting (5%), and nausea (4%). The most frequent adverse reactions (≥3%, all-causality frequency) associated with dose reductions were elevated transaminases (4%), and neutropenia (4%). All-causality adverse events associated with permanent treatment discontinuation occurred in 298 (18%) patients of which the most frequent (≥1%) were interstitial lung disease (1.4%) and elevated transaminases (1%). Additional common adverse reactions occurring in patients treated with crizotinib included, abdominal pain (21%), dysgeusia (21%), leukopenia (15%), anaemia (15%), rash (13%), increased blood creatinine (8%), increased Alkaline Phosphatase (7%), hypophosphataemia (6%), Electrocardiogram QT prolonged (4%), Syncope (3%), ILD (3%, Acute respiratory distress syndrome, Alveolitis, Interstitial lung disease, Pneumonitis), renal cyst (3%). Vision disorder included Diplopia, Halo vision, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual brightness, Visual field defect, Visual impairment, Vitreous floaters. Grade 4 visual field defect with vision loss has been reported in 4 (0.2%) patients. Other less common any grade adverse events in all the clinical trials included decreased testosterone, oesophagitis, gastrointestinal perforation, hepatic failure, cardiac failure. Across all the clinical trials bradycardia with heart beat less than 50beats/min occurred in 12% of patients. **Warnings and Precautions:** 1. Drug induced hepatotoxicity has been observed in Crizotinib clinical trials. Assessment of liver functions including ALT and total bilirubin is recommended every 2 weeks during the first 2 months of therapy, then once a month and as clinically indicated.2. Monitoring the patients for pulmonary symptoms which are indicative of pneumonitis is essential and this drug should be permanently discontinued if diagnosed of treatment-related pneumonitis.3. Caution must be exercised when treating patients with crizotinib who have a known history of or have predisposition for QTc prolongation, or who are taking medications that are known to prolong the QT interval. Periodic monitoring with electrocardiograms and electrolytes should be considered. 4. Avoid Crizotinib in combination with other agents known to cause bradycardia to extent possible. 5. Monitor heart rate and blood pressure regularly in relation to bradycardia. 6. Patients with or without pre-existing cardiac disorders, receiving crizotinib, should be monitored for signs and symptoms of heart failure. 7. Complete blood counts including differential white blood cell counts should be monitored as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs. 8. Crizotinib should be used with caution in patients at risk for gastrointestinal perforation. 9. If patients have severe renal impairment not requiring peritoneal dialysis or haemodialysis, the dose of crizotinib should be adjusted. 10. Patients who experience vision disorder, dizziness, or fatigue should drive or operate machines cautiously. 11. Crizotinib may cause fetal harm when administered to a pregnant woman. Women of childbearing potential who are receiving this drug, or partners of women of childbearing potential receiving this drug, should use adequate contraceptive methods during therapy and for at least 90 days after completing therapy. Women should be advised against breast-feeding or to discontinue crizotinib taking into account the importance of the drug to the mother. 12. The safety and efficacy of crizotinib in pediatric patients has not been established. 13. Concomitant treatment with agents that have CYP3A4/5 induction and inhibition potential should be avoided. **Dosage:**250mg or 200mg capsule of Crizotinib can be administered orally with or without food twice daily. If dose reduction is necessary, then the dose of crizotinib should be reduced to 200 mg to be taken orally twice daily, and if further dose reduction is necessary, then reduce the dosage to 250 mg orally once daily based on individual safety and tolerability. See Full PI for details.

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CRIZALK™ CRIZOTINIB

## Conclusions :

Current work in the liquid biopsy field continues to show great potential utility in the diagnosis and stratification of cancer patients and furthermore exemplifies as surrogate method for monitoring treatment response when compared to the tissue biopsy approach. The ease and frequency made possible by serial liquid biopsy collection offers plenty of advantages compared to standard surgical procedures, especially including the opportunity of more rapid course correction of administering therapies. Though it can't replace standard tissue diagnosis at time of cancer diagnosis but will become important supplementary and companion diagnostic tool very soon and is a reality now.

## RECOMMENDATIONS FOR CANCER PREVENTION

1. Be as lean as possible without becoming underweight.
2. Be physically active for at least 30 minutes every day. Limit sedentary behavior.
3. Avoid sugary drinks. Limit consumption of energy-dense foods.
4. Eat more of variety of vegetables, fruits, whole grains and legumes such as beans.
5. Limit consumption of red meats (such as beef, pork and lamb) and avoid processed meats.
6. If consumed at all, limit alcoholic drinks to 2 for men and 1 for women a day.
7. Limit consumption of salty foods and foods processed with salt (sodium)
8. Don't rely on supplements to protect against cancer.
9. New mothers should breastfeed babies exclusively for up to 6 months and then add other liquids and foods.
10. Post treatment, cancer survivors should follow the recommendations for cancer prevention.

**And always remember- Do not smoke or chew tobacco !!!**

## *About the SoMex Research & Health Pvt. Ltd.*

- It is a clinical research and academic orgazation for promotion of same in Rajasthan.
- SoMex Academic & Research Committee helps medical fraternity & others in evaluating & designing clinical trials & protocols.
- Somex has conducted more than 35 Clinical Trials with diverse indications Including Phase 1 and 2, 3 and BA/BE Studies.
- Somex also designes and conducts Seminars, CMEs & Medical Conferences. It has conducted more than 45 CMEs in various medical fields.
- Conducts Cancer Awareness & Health Survey programs.

## *Recent Activities of Somex Research & Health Pvt. Ltd.*

- Conducting Indian Breast Cancer Conference (Web.: www.ibccjaipur.in)
- Conducted Nerurology Conference on 23 to 24 July, 2017.
- CME on "Multipal Myloma" on 28th July, 2017.
- CME on "Lung Cancer" on 30th June, 2017.
- CME on "NSCLC beyond first line driver mutation negative patients & what's new in ASCO " on 9th June, 2017.
- CME on "Lung Cancer Update" on 7th April, 2017.

**BOOK - POST**

To,_____

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*If undelivered please return to:*
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