Cancer being a genomic disease evolves over time and following drug treatment by successive acquisition of mutations in “driver” and/or “passenger” genes. Thus the uncovering of mutations in cancer cells unlocks the option(s) for targeted treatment for patients for which they would have been unqualified otherwise. The precision oncology which presents expanded treatment options to oncologists and patients fundamentally interrogates alterations of genes in terms of DNA, RNA, proteins and phospho-proteins in an individual patient’s tumor and harness these genomic and proteomic alterations in the background of tumor cell signaling. Thus a decision making in precision oncology wherein a drug or a combination of drugs is matched with an individual patient’s tumor and harness these genomic and proteomic alterations in the background of tumor cell signaling. Thus a decision making in precision oncology wherein a drug or a combination of drugs is matched with an individual patient’s tumor not only considers the mutation of a gene but also the site of the mutation [1, 2] to know the functionality of the mutation along with the accompanying mutations in different genes in the same tumor, Mutational Contextuality.

In the issue number 1 of volume 19, Lancet Oncology, 2018, Cecchini and colleagues from Yale Cancer Center Precision Medicine Tumor Board reported a thought-provoking snapshot entitled “Two Patients, one targeted therapy, different outcomes” [3]. The crux of this “perspectives” communication was to describe a radically opposite clinical outcome in two patients, carrying mutations in the same driver gene, ATM, when treated with one targeted therapy, Olaparib. Olaparib treatment stabilized the disease for more than six months in the patient with prostate cancer, while the outcome of the patient with sarcoma was dismal. Scientific explanation upon in-depth interrogation of the clinical outcomes and the background genomic alterations in these two patients strongly indicates a deterministic role of contextuality of an accompanying actionable genomic alteration(s) in tumor progression.

Although both tumors were ATM mutation-driven, they differed in their contextuality of ATM-mutation. The patient with prostate cancer clinically responding to Olaparib treatment expressed TPRRSS2-ERG fusion, a common genomic alteration of prostate cancers in addition to ATM-mutation. Expression of TPRRSS2-ERG fusion provides a mechanistic rationale for inhibition of PARP in ETS gene fusion-positive prostate cancer [4]. ERG interacts with PARP1 and DNA-PKcs in a DNA-independent manner (through the ERG-ETS domain amino acid Y373) and with Ku70 and Ku80 in a DNA-dependent way (through its C-terminal region) [5]. ERG can regulate gene transcriptional activity in a protein interaction dependent manner, which is most likely coupled with DNA binding transcriptional regulation [5]. The expression of TPRRSS2-ERG fusion in addition to the ATM-mutation in the patient with prostate cancer led to a higher level of oncogenic-dependency of his tumor on the DNA-damage repair pathway and hence his better clinical response to Olaparib. Thus the event that both the patients bearing the same pathogenic mutation of ATM bore an opposite clinical outcome to Olaparib can be explained by the fact that genomically the tumor of the patient with prostate cancer was inherently more dependent on DNA damage repair system than from the patient with sarcoma.
The deterministic role of contextuality of an accompanying actionable genomic alteration(s) is furthermore evident from the fact that the patient with sarcoma carrying ATM mutation who progressed on Olaparib also had additional Q61K hotspot mutation of NRAS. Q61K oncogenic mutation of NRAS is responsible for the enhanced GTP-bound activated state (insensitive to regulation by GTPase activating proteins, GAPs) of NRAS which leads to activation of the RAS-RAF-MAPK pathway, important in the control of cell proliferation, survival and differentiation. The failure of Olaparib to achieve the desired clinical outcome in sarcoma patient with the ATM-mutated tumor can be explained by accompanying oncogenic mutation of NRAS at Q61K suggesting that in this case, Olaparib is necessary but not sufficient. Studies reported encouraging results describing rational combination therapy with PARP and MEK inhibitors in RAS-mutated cancers [6] and sensitization to DNA damaging agents in the pancreas and ovarian cancer models following MEK inhibition [7].

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Avera Cancer Institute, Sioux Falls, South Dakota.

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Address correspondence to: Pradip De, Translational Oncology Laboratory, Avera Cancer Institute, Sioux Falls, SD, USA; Department of Internal Medicine, SSOM, University of South Dakota, SD, USA. E-mail: Pradip.De@avera.org

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