Am J Cancer Res 2019;9(3):628-629
www.ajcr.us /ISSN:2156-6976/ajcr0092309

Letter to Editor

Decision making in precision oncology: an issue of mutational contextuality

Nandini Dey[1,2], Pradip De[1,2]

[1]*Translational Oncology Laboratory, Avera Cancer Institute, Sioux Falls, SD, USA;* [2]*Department of Internal Medicine, SSOM, University of South Dakota, SD, USA*

Received February 6, 2019; Accepted February 15, 2019; Epub March 1, 2019; Published March 15, 2019

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 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 *TMPRSS2-ERG* fusion, a common genomic alteration of prostate cancers in addition to *ATM*-mutation. Expression of *TMPRSS2-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 *TMPRSS2-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].

Acknowledgements

Avera Cancer Institute, Sioux Falls, South Dakota.

Disclosure of conflict of interest

None.

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

References

[1] Dey N, Williams C, Leyland-Jones B and De P. Mutation matters in precision medicine: a future to believe in. Cancer Treat Rev 2017; 55: 136-149.

[2] Dey N, Williams C, Leyland-Jones B and De P. Promise of precision medicine in cancers: lessons learned. S D Med 2017; 70: 486-490.

[3] Cecchini M, Walther Z, Sklar JL, Bindra RS, Petrylak DP, Eder JP and Goldberg SB. Yale cancer center precision medicine tumor board: two patients, one targeted therapy, different outcomes. Lancet Oncol 2018; 19: 23-24.

[4] Brenner JC, Ateeq B, Li Y, Yocum AK, Cao Q, Asangani IA, Patel S, Wang X, Liang H, Yu J, Palanisamy N, Siddiqui J, Yan W, Cao X, Mehra R, Sabolch A, Basrur V, Lonigro RJ, Yang J, Tomlins SA, Maher CA, Elenitoba-Johnson KS, Hussain M, Navone NM, Pienta KJ, Varambally S, Feng FY and Chinnaiyan AM. Mechanistic rationale for inhibition of poly (ADP-ribose) polymerase in ETS gene fusion-positive prostate cancer. Cancer Cell 2011; 19: 664-678.

[5] St John J, Powell K, Conley-Lacomb MK and Chinni SR. TMPRSS2-ERG fusion gene expression in prostate tumor cells and its clinical and biological significance in prostate cancer progression. J Cancer Sci Ther 2012; 4: 94-101.

[6] Sun C, Fang Y, Yin J, Chen J, Ju Z, Zhang D, Chen X, Vellano CP, Jeong KJ, Ng PK, Eterovic AKB, Bhola NH, Lu Y, Westin SN, Grandis JR, Lin SY, Scott KL, Peng G, Brugge J, Mills GB. Rational combination therapy with PARP and MEK inhibitors capitalizes on therapeutic liabilities in RAS mutant cancers. Sci Transl Med 2017; 9.

[7] Vena F, Jia R, Esfandiari A, Garcia-Gomez JJ, Rodriguez-Justo M, Ma J, Syed S, Crowley L, Elenbaas B, Goodstal S, Hartley JA and Hochhauser D. MEK inhibition leads to BRCA2 downregulation and sensitization to DNA damaging agents in pancreas and ovarian cancer models. Oncotarget 2018; 9: 11592-11603.