doi: 10.3978/j.issn.2095-6959.2021.11.001
View this article at: https://dx.doi.org/10.3978/j.issn.2095-6959.2021.11.001

· International Clinical and Pathological Column ·

Are there markers for exceptional responders available for attending pathologists?

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Comment on: Inoue Y, Yoshimura K, Nishimoto K, *et al.* Evaluation of programmed death ligand 1 (PD-L1) gene amplification and response to nivolumab monotherapy in non-small cell lung cancer[J]. JAMA Netw Open, 2020, 3(9): e2011818.

In the records of the recent rampant clinical trials, people have noticed there is a fraction, though small, who have extremely good responses to the drugs. The definition of this population "Cancer exceptional responder" is proposed and feasibility study has been launched[1]. Definition there is not particularly hard ones. Classical example is one of 14 bladder cancer patients who participated in Everolimus phase 2 trial, had complete response, and subsequent analysis of DNA of those patients revealed that they had inactivation mutations in *TSC1* and *NF2*, both of which were mTOR regulators[2]. As this example showed, the most important impetus toward enthusiasm to find out the tumors highly responsive to therapy is popularity and accessibility to clinical usage of the next generation sequencing. Recently, Wheeler *et al.*[3] investigated genomics of 111 exceptional responders and applied various omics approach including epigenetics and microenvironment to the specimen. One of the main mechanisms is proposed to explain this extremely good responsiveness to the drug is oncogene addiction[4]. The best example would be a HER2-Herceptin story. This achievement starting from one clinicopathological data published in *Science*[5] which draw the first attention from the oncologists' community giving them perspectives on DNA markers can be predictive for prognosis in clinical settings. The comprehensive success story as to Herceptin has been vividly expounded in the popular book[6]. When any cancer is very addictive on a certain oncogene, targeting it is a very promising approach to combat this particular cancer with particular type. The particular type, in this case the cases having HER2 amplification were revealed to be exceptionally good responder to Herceptin. Focal amplification, such as the one at HER2 locus, is a common feature of common cancers, and fluorescence in situ hybridization (FISH) modified for formalin fixed paraffin embedded tissue[7-8] became a feasible technique in pathology laboratories in community hospitals and reference laboratories all over the world. In addition to copy number estimation algorism on the next generation sequencing data, FISH is widely accepted procedure to identify the focal chromosomal amplification[9-11]. Recently an emerging target, PD-L1, is also a locus frequently amplified in non-small cell lung cancer (NSCLC)[12]. The copy number information of PD-L1 using FISH from FFPE is sometimes more stable than immunostaining and evade the concerns caused by heterogeneity of IHC in tumors[13]. Then can we follow the suit of HER2-Hereptin achievements in PD-L1 and nivolumab? The group of Shizuoka prefecture in Japan reported that the answer is probably "yes"[14]. The project, supported by ONO PHARMACEUTICAL CO., Ltd., started with calling for the pathologists to collect blocks, on which the first pathological diagnosis of NSCLC had been made, of the patients who subsequently received nivolumab. As previous guideline allowed indication of nivolumab for squamous cell carcinoma is not dependent on the immunostaining score of PD-L1 antibody, different from in case of non-squamous cell carcinoma and pembrolizumab[15]. Generally, the threshold of 1%[16-18] are accepted in practice. The blocks usually contained

Submitted May 28, 2021. Accepted for publication Jun 08, 2021.

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several pieces of trans bronchial lung biopsy (TBLB) tissues and some of them were taken into recipient block of tissue microarray blocks. This logistics were actually painstaking to convince the pathologists to persuade the importance of this project. Collecting small pieces into one block is safest procedure both for the efficient test and preservation of the small amounts of tissues, so that the original attending physician and pathologists can easily access to the tissues on the exact address on the tissue microarray. The 200 cases were recruited and blind test revealed 5 out of them had amplification of PD-L1. Subsequent uncovering was remarkable. This group (amplification) showed almost horizontal lines in Kaplan Meyers graph as compared to polysomy and disomy cases.

In addition to the preliminary nature of this work, that is too small numbers were prominent in a too small cohort, the design of the prospective work must be make up. Yet, the recent trend is combination therapy trial[19] which does not include this kind of stratification of the cohort. Therefore, the retrospective analysis would be informative and realistic to all the tumor tissues in the subject who had received immuno-checkpoint inhibitors ICIs). Actually, some portion of the triple negative breast cancer sometimes had PD-L1 amplification and the effectiveness of ICIs must be validated[20]), and there would be other predicting markers and drugs targeting them in addition to JAK2 amplification nearby and drugs related to its signaling pathway.

The percentage of PD-L1 amplification is low, 1–3%, but this subpopulation is not too small in the era of N-of-1 precision medicine.

Acknowledgments

Funding: Some of the content is supported by the SRF.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Clinical and Pathological Research* for the series "International Clinical and Pathological Column". The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.3978/j.issn.2095-6959.2021.11.001). The series "International Clinical and Pathological Column" was commissioned by the editorial office without any funding or sponsorship. The author serves as an unpaid editorial board member of *Journal of Clinical and Pathological Research* from Apr 2021 to Mar 2023. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Sugimura H. Are there markers for exceptional responders available for attending pathologists?[J]. Journal of Clinical and Pathological Research, 2021, 41(11): 2497-2499. doi: 10.3978/j.issn.2095-6959.2021.11.001