

Targeting the PD-1 Pathway in Cancer Patients: The Immune System RELOADED

Reyad Dada^{1,2}

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1 King Faisal Specialist Hospital and Research Center, Jeddah, Kingdom of Saudi Arabia

2 College of Medicine, Al-Faisal University, Riyadh, Kingdom of Saudi Arabia

Corresponding author: Reyad Dada

✉ rdada@kfshrc.edu.sa

MD PhD, Department of Oncology MBC J-64, King Faisal Specialist Hospital and Research Center, P.O. Box 40047, Jeddah 21499, Kingdom of Saudi Arabia.

Tel: +966-12-6677777 ext. 64065

Fax: +966-12-6677777 ext. 64030

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Introduction

Recent studies report on interesting clinical activity of nivolumab in heavily pretreated patients with classical Hodgkin lymphoma (cHL) [1] and different subtypes of non-Hodgkin lymphoma (NHL) [2]. In latter one responses were documented in 40%, 36%, 15%, and 40% in patients with follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), mycosis fungoides, and peripheral T-cell lymphoma, respectively. Duration of response (DOR) in Lesokhin et al. [1] work exceeded remarkable one year for 2/3 patients who achieved a complete remission (CR) with nivolumab. Interestingly, PD-L1 and PD-L2 genetic alterations were detected only in 11% (3/27) of the tested samples in the study. However, the small sample size and heterogeneity of NHL subtypes in this study may not lead to reliable conclusion on the real incidence of this alteration. In another recently published study the frequency of 9p24.1 alteration in DLBCL was only 5% [3] while it was 33% (2/6) in Lesokhin et al. work [2]. This is in contrast to higher rate of 9p24.1/CD274(PD-L1)/PDCD1LG2 (PD-L2) alterations reported in 97% (105/108) of patients with cHL [3,4]. The incidence of 9p24.1 amplification was more common in patients' with advanced stages cHL. This variability of 9p24.1 exhibition between different lymphoma subtypes and even within the same type in cHL reflects the complexity around this alternation and the need of further research in larger and more homogenous patient population with well elected patients' eligibility criteria.

We are entering new area of treatment options that were beyond our imagination a decade ago. The discoveries around checkpoint inhibitors are revolutionizing our understanding of tumor biology and how to halt cancer progression. It is quit more astonishing to see such amazing high response rates in heavily pretreated lymphoma patients. It has science fiction aura as in "The Matrix Reloaded" movie series. In these movies a computer software (The Matrix) protected by a self-duplicating program (agent Smith) tries to destroy the last survivors of mankind. "Neo", the main actor, discovers his superpowers and ability to recognize the code embedded in the Matrix. The "Keymaker" in the film guided Neo to the right path into the Matrix. But first of all, Neo had to neutralize

agent Smith and eventually defeating him. Thereafter, Neo gained access to the Matrix and was able to reload the system.

We treated three heavily pretreated Hodgkin lymphoma patients (failed up to nine lines of chemotherapy including brentuximab, vedotin and autologous stem transplantation) with single agent nivolumab. All 3 patients achieved CR radiological response associated with significant improvement of performance status and quality of life.

Our anecdotal experience coupled with the relatively limited data in the literature create an atmosphere of anticipation to how patients with relapsed lymphomas will be managed in the near future. The next challenge will be how to identify those patients who are likely to respond and gain meaningful DOR and thus likely to gain maximum clinical benefit. Furthermore, relation between efficacy of different inhibitors of PD-1 pathway and 9p24.1 alteration shall be further illuminated.

PD-1 inhibitors reload the immune system against cancer. To draw an analogy with "The Matrix" series, PD-1 receptor can be thought of as the "Keymaker" in the film which is being kept under control by PDL-1 (agent Smith) on the tumor cells (The Matrix). PD-1 inhibitor (Neo) neutralizes the inhibitory effect of PDL-1 (agent smith) and reloads the immune system against the cancer (The Matrix).

Welcome to a new real world!

References

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