

Rational Design of Combinations for the Treatment of Advanced Cancer

Takefumi Komiya*

Division of Medical Oncology, University of Kansas Medical Center, USA

*Corresponding author: Takefumi Komiya, University of Kansas Cancer Center, 4350 Shawnee Mission Parkway, MS 6004, Fairway, KS-66205, USA, Tel: 9135884709; Fax: 9135884394; E-mail: tkomiya@kumc.edu

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Short Communication

Despite our enormous effort and progress in medicine, cancer remains a top health issue worldwide. According to recent statistics, more than eight million people annually succumb to the disease in the world [1]. It is clear that we must work much harder in order to eliminate this disease in the next several decades. We have a hope, however, that can encourage us to do so and move forward: cancer immunotherapy. Systemic immunotherapy for the treatment of cancer has been investigated for many decades and has struggled to become a key player in that regard. Before new immunotherapy such as immune checkpoint inhibitors became available in human studies, the use of immunotherapy for advanced malignancy was very limited. Although cytokine therapies such as IL-2 were available in clinic, their indications were limited to melanoma and renal cell carcinoma [2]. Unclear survival benefit in both disease settings and poor tolerability made caregivers hesitant to prescribe these agents.

Long-lasting nihilism in cancer immunotherapy came to an end when clinical studies using therapeutic cancer vaccine and checkpoint inhibitors demonstrated their efficacy and tolerability [3,4]. Several checkpoint inhibitors targeting CTLA4 and PD-1/PD-L1 have already achieved FDA approval for the treatment of advanced cancers. The use of anti-CTLA4 inhibitor ipilimumab is currently limited to advanced melanoma, whereas that of anti-PD-1/PD-L1 inhibitors covers non-small cell lung cancer, head/neck, renal cell, bladder, melanoma, and likely more in a few years [4-7]. Several indications are based on positive phase III studies with survival benefit over standard treatment [8-11].

However, how to predict therapeutic efficacy of anti-PD-1/PD-L1 therapy in order to select patients has been a great controversy over the last few years. Studies using pembrolizumab demonstrated that patients with high PD-L1 level in tumor had better tumor response and survival over those with lower/no PD-L1 expression [11]. However, this correlation was not always seen in other studies. Variations in methodology in PD-L1 detection may lead to different and inconsistent outcomes. The use of different antibodies, cut-off, and other technical issues may play a role in the discrepancy. Therefore, establishment of universal method to detect PD-L1 expression has been a matter of debate. In addition to PD-L1 expression, several other potential mechanisms and markers were proposed for predicting efficacy of anti-PD-1/PD-L1 inhibitors. They include overexpression of PD-L1 in tumor related immune cells, microsatellite instability, mutational load, and others [12-15]. Although these markers may select patient population who more likely benefit from anti-PD-1/PD-L1 inhibitors, they have not led to development of new therapeutic management. Overcoming drug resistance has not yet been addressed by rational combination studies.

More recently, Peng et al. have demonstrated that loss of tumor suppressor gene *PTEN* is associated with better clinical response to anti-PD-1 therapy in patients with advanced melanoma [15]. *PTEN* is a negative regulator of oncogenic pathway mTOR in which loss-of-function mutation in *PTEN* is commonly seen in various human cancers. Targeting their upstream molecule PI3K enhanced activity of anti-PD-1 inhibitor in a mouse xenograft model. Lastwika et al. have also demonstrated that rapamycin, a mTOR inhibitor that is commonly used for post-organ transplant setting, synergistically suppressed tumor growth in combination with anti-PD-1 antibody in their Kras-driven transgenic lung cancer model [16]. mTOR inhibitors such as rapamycin can suppress regulatory T cells (Treg) and decrease PD-L1 expression in tumor cells *in vivo* [16,17]. They can also induce autophagy which plays a key role in T-cell mediated apoptosis of cancer cells [15]. These lines of evidence support the combination therapy of anti-PD-1 and anti-PI3K/AKT/mTOR pathway inhibitors.

Discovery of oncogenic drivers such as EGFR in non-small cell lung cancer revolutionized therapeutic management in several clinical settings [18]. Despite a number of clinical trials investigating combination strategy over the decade, combination therapy does not generally provide better outcome over single agent alone. For instance, addition of chemotherapy to EGFR inhibitor in lung cancer failed to show any benefit in multiple phase III trials [18,19]. Combination therapies with multiple targeted agents have rarely achieved any new indication. Although numerous studies are now combining checkpoint inhibitors with chemotherapy, our history suggests simple combination of two active treatment modalities will unlikely yield a great success. Only studies that were designed based on scientific evidence will likely hold the promise. Clinical researchers need to work with scientists closely for designing rational trials.

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