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**Combined targeted therapy and immunotherapy for cancer treatment**

Guo CX *et al*. Combined therapy for cancer

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**Abstract**

Although targeted therapies and immunotherapies have been effective against several malignancies, the respective monotherapies are limited by low and/or short-term responses. Specific inhibitors of oncogenic signaling pathways and tumor-associated angiogenesis can activate the anti-tumor immune responses by increasing tumor antigen presentation or intratumor T cell infiltration. Additional insights into the effects and mechanisms of targeted therapies on the induction of anti-tumor immunity will facilitate development of rational and effective combination strategies that synergize rapid tumor regression and durable response. In this review, we have summarized the recent combinations of targeted therapies and immunotherapies, along with the associated clinical challenges.

**Key Words:** Cancer; Targeted therapy; Immunotherapy; Combined treatment

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**Core Tip:** There has been considerable interest in combining systemic and immune-related therapies for the anti-tumor treatment of cancer. Additional insights into the effects and mechanisms of targeted therapies on the induction of anti-tumor immunity will aid the development and design of effective strategies, with the synergistic potential for rapid tumor regression and a durable response. Targeting specific signaling pathways may help in overcoming the mechanisms of immunotherapy resistance. We briefly review the immunomodulatory effects of targeted therapies and immunotherapies and discuss the obstacles associated with them, which may be useful for the development of novel basic research or clinical trials.

**INTRODUCTION**

Recent advances in targeted therapies and immunomodulatory anti-cancer therapies have revolutionized the standard of care for several malignancies. Unlike traditional chemo- or radiation therapies that indiscriminately kill the rapidly dividing cells, the aim of cancer immunotherapy is to activate effector T cells against cancer-specific antigens, which selectively clear the malignant cells. The immune checkpoint inhibitors (ICIs) target the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathways that are constitutively activated in cancer cells and enable them to evade an immune response. However, this strategy is limited by the risk of autoimmunity and overall lower response rates[1-4]. In addition, studies show that while immunotherapeutic approaches can potentially achieve relatively long-term disease control, the median duration of achieving peak response is significantly longer, resulting in delayed tumor regression[5]. Therefore, there is an urgency to develop novel immunotherapeutic strategies against cancer in order to achieve a strong and durable immune response.

Several oncogenic mutations have been identified over the past decades that not only drive the malignant progression of tumors but are also potential therapeutic targets[6-9]. However, the high response rates elicited by drugs targeting these mutations is offset by the short duration of response, resulting in tumor progression within a median duration of 6 mo[10]. Combination of immunotherapy with signal transduction inhibitors has achieved positive results in terms of improving patient response, although resistance is a major issue, and most patients relapse within a year[11]. Therefore, studies have increasingly focused on the resistance mechanisms that reactivate oncogenic pathways or stromal interactions in order to develop more effective drugs[12]. In addition, some drugs not only target tumor angiogenesis and/or cancer cell growth but also facilitate immune recognition, thereby sensitizing the cancer cells to immunotherapy[13].

The major obstacle to generating an effective anti-tumor immune response is the immunosuppressive tumor microenvironment (TME), which is the result of sparse tumor-specific T cells and multiple immunosuppressive factors[14]. Studies increasingly show that the optimal therapeutic efficacy of several anti-neoplastic agents is largely determined by their ability to influence the tumor–host interaction, including activation of an immune response against the cancer cells[15]. Pre-clinical reports in fact provide a solid rationale for combining tumor-targeted and immunotherapies in order to enhance tumor clearance[16], and several ongoing clinical trials are assessing the potential synergistic effects of both approaches (Table 1). In this review, we have summarized several combination therapies and their mechanisms and discussed the clinical considerations and challenges of these strategies.

**Strategy 1: Combination of epigenetic therapies with immunotherapy**

Epigenetic gene silencing or constitutive activation are frequent during cancer initiation and progression and are regulated by reversible DNA methylation and histone acetylation. Therefore, DNA and histone modification pathways are promising targets for cancer therapy[17,18]. The DNA methyltransferase inhibitors (*e.g.,* azacitidine) and histone deacetylase inhibitors (*e.g.,* entinostat) activate both intrinsic and extrinsic pathways of apoptosis in the malignant cells[19]. In addition, these epigenetic modulators enhance tumor cell recognition and immunogenicity by upregulating the major histocompatibility complex molecules and natural killer cell receptor ligands and increasing the activity of proinflammatory cytokines[20]. For instance, histone deacetylase inhibitors augmented the anti-tumor activity of high dose interleukin-2 against the modified lung cancer cell line TC-1 and the Renca murine kidney cancer model[21,22]. In addition, the combination of entinostat and azacitidine with PD-1 and CTLA-4 checkpoint blockers led to complete tumor regression and prevented metastasis in 4T1 tumor mouse models. Apart from directly inhibiting tumor growth, this combination therapy enhanced the anti-tumor response by decreasing the number of granulocytic myeloid-derived suppressor cells in the TME[23]. The efficacy of antigen-specific adoptive cell transfer in the pmel-1 melanoma mouse model was enhanced with the inclusion of epigenetic drugs[24]. Furthermore, histone deacetylase inhibitors used in combination with the anti-CD137 or anti-CD40 antibodies stimulated antigen cross-presentation and enhanced the proliferation and survival of CD8+ T cells against subcutaneous tumors[25]. Several clinical trials on the effect of azacitidine and entinostat in combination with ICIs against lung cancer or metastatic melanoma are currently in the recruiting stage.

**Strategy 2: Combination of MAPK–MEK inhibitors with immunotherapy**

The mitogen-activated protein kinase (MAPK) signaling axis is a critical driver of tumorigenesis, and nearly half of all malignant melanomas harbor the mutant B-Raf proto-oncogeneV600E (BRAF)[6], which has been associated with immune escape and an immunosuppressive TME. The targeted inhibition of MAPK pathway signaling with BRAF and mitogen-activated protein kinase kinase (MEK) inhibitors can counteract this immunosuppressive effect[26], indicating a potential synergy between targeted therapy and immunotherapy. Indeed, MAPK pathway inhibition in both melanoma cell lines and tissues increases the expression of melanoma differentiation antigens, which in turn primes the antigen-specific T cells[27,28]. MAPK inhibitors can also augment anti-tumor immunity by increasing intratumoral T cell infiltration and altering the immune status of the TME, likely through blocking signals that elicit T cell exhaustion or apoptosis and downregulating immune suppressive factors or chemokines[29].

There is also evidence that pharmacological inhibition of MAPK signaling augments the effect of ICIs. In a BRAFV600E-driven murine model of melanoma, combination of a BRAF inhibitor and adoptive transfer of engineered T cells resulted in stronger anti-tumor responses compared to either therapy alone[30]. Interestingly, immune checkpoint blockade also augmented the effect of BRAF inhibitors against metastatic melanoma, in addition to activating the tumor-infiltrating T cells[31,32]. In patients with metastatic colorectal cancer, the MEK inhibitor cobimetinib synergized with the anti-PD-L1 antibody atezolizumab to enhance anti-tumor efficacy.

**Strategy 3: Combination of VEGF inhibitors with immunotherapy**

Vascular endothelial growth factor A (VEGFA) and its receptors (VEGFRs) are crucial for early tumor angiogenesis. Therapeutic agents targeting VEGFA or VEGFRs, including bevacizumab, sorafenib and sunitinib, are currently approved for the treatment of several malignancies[33]. In addition to hindering the recruitment and infiltration of T cells and other immune cells into the tumor[34], high levels of VEGFA can also directly inhibit the anti-tumor immune response by suppressing dendritic cell differentiation and activity and upregulating checkpoint molecules on CD8+ T cells[35,36]. Studies on mouse models show a significant association between normalization of tumor vasculature with VEGFA/VEGFRs inhibitors and positive immunological changes in neoplastic tissues[37,38].

In addition, clinical studies have also reported that VEGFA and VEGFR inhibitors synergize with immunotherapies to enhance anti-tumor immune responses and the associated clinical benefits. For example, the autologous cell-based vaccine sipuleucel-T and bevacizumab enhance tumor antigen presentation in patients with recurrent early-stage prostate cancer[39]. Likewise, bevacizumab augmented the efficacy of anti-CTLA-4 antibody ipilimumab in advanced metastatic melanoma and increased intratumor immune cell infiltration, which translated to greater clinical responses[40]. A synergistic interaction has also been observed between bevacizumab and anti-PD-L1 therapy in patients with renal cell carcinoma. The combination of immunotherapies with other tumor vasculature modulators, such as the angiopoietin/Tie2 signaling pathway, is also a promising strategy for cancer therapy.

**Strategy 4: Combination of PI3K-AKT-mTOR signaling inhibitors with immunotherapy**

The phosphoinositide 3-kinase (PI3K)-protein kinase B-mechanistic target of rapamycin (mTOR) signaling pathway is critical to oncogenic progression as well as the differentiation, homeostasis and functions of effector T cells and regulatory T (Treg) cells[41]. Phosphatase and tensin homolog deficiency and subsequent activation of PI3K signaling in melanoma or glioblastoma multiforme patients correlate with increased expression of PD-L1 and immune evasion, resulting in resistance to ICIs. Furthermore, preclinical studies show that a selective PI3K inhibitor improves the efficacy of immune checkpoint blockade by augmenting T cell trafficking and/or increasing T cell-mediated tumor cell killing[42,43]. Inhibition of PI3K in Treg cells also facilitates anti-tumor immune activation in preclinical models of melanoma and lymphoma[44], indicating the therapeutic potential of combining PI3K inhibition with PD-1/PD-L1 blockade. In fact, the PI3K-specific inhibitor idelalisib has been tested clinically along with PD-1 blockade in patients with relapsed chronic lymphocytic leukemia and indolent lymphoma[45,46]. Although mTOR inhibitors are often used for immune suppression after organ transplantation, there are reports indicating a positive effect on anti-tumor CD8- effector T cell expansion and the long-lived memory response[47-49]. The therapeutic effects of mTOR inhibitor rapamycin or its derivative were augmented by anti-cancer vaccine (*e.g.,* HSP110) or an agonistic CD40 monoclonal antibody in mouse syngeneic graft models of renal cell carcinoma and melanoma through increased tumor infiltration of T cells[50,51].

**Challenges of combination therapies**

Several combinations of tumor-targeted and immunotherapies are currently undergoing clinical evaluation. However, it is vital to determine the proper sequence, dosage and timing of the individual therapies in order to minimize toxicity and optimize efficacy as well as select appropriate endpoints to assess therapeutic efficacy.

The potential cumulative toxicity of these combination therapies is a major challenge. For instance, several clinical trials have been terminated on account of unpredicted hepatotoxicity[52]. While PD-1/PD-L1 blockade is associated with lower toxicity compared to anti-CTLA-4 monotherapy, it is unclear whether this will translate to combination therapies with other targeted agents[1-3]. The combination of MAPK inhibitors and immunotherapies also result in adverse effects that are typically assuaged once the treatment is withdrawn. Nevertheless, the potential toxicity of these combination treatments should be evaluated and monitored carefully during clinical trials.

In order to minimize unexpected toxicity due to novel targeted agents (*e.g.*, CDK4, PI3K, MDM2, FGFR and c-MET inhibitors) and immunotherapeutic drugs (*e.g.*, TIM-3, LAG-3, B7-H3, OX40/OX40L and ICOS/ICOSL inhibitors)[5,53], the proper sequence, schedule and duration of the treatment regimens should be determined. Considering the rapid clinical response to targeted drugs, they would likely be preferred for the initial regimen against advanced tumors. Preliminary data point to a narrow window of approximately 10–14 d post BRAF-targeted therapy for maximum T cell recruitment and activation. The beneficial effects of BRAF inhibitors on the melanoma TME, such as increased infiltration of T cells in the tumors and overexpression of melanocyte differentiation antigens, are short lived and disappear within 4 wk of treatment and may even exacerbate tumor progression[32,54]. Therefore, the immunomodulatory agent should be introduced early during the treatment to prevent relapse and disease progression. Nonetheless, these findings are extracted from limited data and need further validation in *in vivo* murine models and clinical trials.

The mTOR inhibitors can have a dual effect on immune cells, depending on their dosage and treatment duration. For example, rapamycin promotes anti-tumor immune response when administered at low doses after immunization, T cell receptor stimulation or under homeostatic conditions[55], whereas high-doses given prior to the vaccine may expand the immunosuppressive Treg cell population[56]. In addition, a 6 wk regimen of everolimus before influenza immunization is clinically tolerable and can enhance immune response by decreasing the percentage of PD-1-expressing peripheral CD4+ and CD8+ T cells[57]. Thus, short-term administration of low dose mTOR inhibitor is potentially immunostimulatory. Since anti-tumor immunity is affected by prepriming of T cells, the metabolic state of Treg cells and the TME[55,56], the combination of low-dose mTOR inhibition with ICIs warrants further investigation.

Some oncogenic pathways, such as the MAPK pathway, are also critical to normal immune functions. Therefore, a potential drawback of targeted therapy (*e.g.*, MEK inhibitors) is general immunosuppression, which can increase the risk of infections. In fact, some preclinical studies have reported impaired T cell proliferation and function by MEK inhibitors. However, no significant differences were seen in the number of infiltrating T lymphocytes in patients treated with BRAF + MEK inhibitors compared to BRAF inhibitor alone. Furthermore, recent preclinical data indicate that MEK inhibitors are compatible with checkpoint inhibitors[29,32]. Thus, the effect of MAPK pathway inhibitors and immunomodulators on immune cell populations need to be analyzed further.

The appropriate endpoints for assessing the efficacy of any regimen are another challenge in designing and executing clinical studies. A small percentage of patients undergoing immunotherapy may have a delayed or complex response that some patients were observed to have new lesions before a response followed by immunotherapy, whereas, in other patients, characterized by an initial increase in the size or volume of their lesions, they became smaller[58-60]. This phenomenon is evidence of pseudo-progression resulting from significant immune cell infiltration into the tumor. In such cases, the Response Evaluation Criteria in Solid Tumors cannot be used to define therapeutic response, since an increase in tumor size or the development of new lesions require modifications in the regimen. Taking into account the immune-related response, clinical trials on the combination of targeted therapies and immunotherapies need a modified approach for evaluating clinical benefit.

Novel combination treatment strategies rely on the identification of predictive biomarkers and establishing biological proof of concept of therapeutic efficacy. However, evidence of a biological role of the potential targets may not be related to the actual anti-tumor mechanism in combination therapies, and the effects can differ between peripheral blood *vs* tumor cells as well as in different immune cell subsets. In addition, the biological effects established in single-agent studies may be altered when combined with immunotherapies, even in the absence of any correlation with clinical response[61]. For example, T cell blockade by MEK inhibitors may not be clinically relevant since the number of infiltrating T lymphocytes is similar in patients receiving combined BRAF–MEK inhibitor or BRAF inhibitor monotherapy[32]. This is a factor that can complicate the selection of optimal dose and schedules for phase II and III trials.

The efficacy of current immune-based therapies is largely dependent on the pre-existing, active anti-tumor inflammatory response. Therefore, additionally enhancing antigen presentation by tumor cells and improving the function of immune cells can markedly increase anti-tumor activity. For example, drugs that enhance T cell trafficking and infiltration into the TME can augment the effect of anti-PD-1/anti-PD-L1 blockade, whereas increasing tumor cell antigenicity or dendritic cell activity may synergize better with anti-CTLA-4 antibodies. This is related to the different mechanisms of PD-1/PD-L1 and CTLA-4 signals, which respectively target T cell killing of tumor cells and T cell priming in the lymph nodes[16]. The effect of targeted therapies on tumor cell growth, immune system and stromal cell functions depends on the tumor type. Therapeutic strategies that stimulate a *de novo* innate immune response in tumors lacking immune cell infiltration can possibly be effective against a wide range of tumors. Furthermore, augmenting immune priming and increasing the expression and presentation of tumor-derived antigens or neoantigens can synergize effectively with therapeutic agents that modulate T cell functions and reverse the immunosuppressive state of the TME. Local radiation therapy also complements immunotherapy by stimulating the release of tumor-associated antigens that prime immune cells and destroying the immunosuppressive tumor-supporting stroma. A recent clinical trial reported marked therapeutic effects of combining local irradiation and ipilimumab with PD-1 blockade in patients with melanoma[62].

**CONCLUSION**

Several anti-tumor targeted therapies can sensitize cancer cells to immunotherapy. In addition, the rapid response of targeted therapies can synergize with the more durable response of immunotherapy. Further investigation is needed on the potential immune-modulatory effects of these combination therapies in order to optimize therapeutic efficacy. Additional clinical trials are also needed to determine the toxicity and sequence of combination therapies.

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**Table 1 Clinical trials combining targeted therapies and immunotherapies**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Target** | **Targeted Therapy** | **Immunological mechanisms** | **Immunotherapy** | **Indication** | **Phase** | **Number Enrolled** | **NCT number** |
| DNMT | Azacitidine | Targeting PD-1 on T cells | Pembrolizumab | HR-MDS | II | 40 | NCT03094637 |
| Azacitidine | Induce tumor-cell-specific immunity | Peptide vaccination | AML | I | 15 | NCT02750995 |
| HDAC | Entinostat | Targeting PD-L1 on tumor cells | Nivolumab | CCA/PDAC | II | 54 | NCT03250273 |
| Entinostat | Targeting PD-1 on T cells | Pembrolizumab | MIBC | II | 20 | NCT03978624 |
| Entinostat | Targeting PD-L1 on tumor cells | Atezolizumab | HER2- breast cancer | I | 126 | NCT03280563 |
| MEK | Binimetinib |  | Pembrolizumab | NSCLC | I | 40 | NCT03991819 |
| & | Dabrafenib | Targeting PD-1 on T cells | Pembrolizumab | Melanoma | II | 60 | NCT02858921 |
| BRAF | +Trametinib |  |
|  | Combimetinib |  | Atezolizumab | Melanoma | II | 30 | NCT03554083 |
|  |  |
|  | Targeting PD-L1 on tumor cells |
|  | Combimetinib |  | Atezolizumab | NSCLC | II | 48 | NCT03660701 |
|  | Vemurafenib |  | Atezolizumab | Melanoma | II | 90 | NCT02303951 |
|  | +Cobimetinib |  |
| VEGF | Lenvatinib |  | Pembrolizumab | Hepatobiliary tumors | II | 50 | NCT03895970 |
| Ziv-Aflibercept | Targeting PD-1 on T cells | Pembrolizumab | Solid tumors | I | 78 | NCT02298959 |
| Bevacizumab |  | Atezolizumab | HNSCC | II | 110 | NCT03818061 |
| Targeting PD-L1 on tumor cells |
| Ramucirumab |  | Atezolizumab | NSCLC | II | 21 | NCT03689855 |
| PI3K | Duvelisib |  | Pembrolizumab | HNSCC | I/II | 30 | NCT04193293 |
| Idelalisib | Targeting PD-1 on T cells | Pembrolizumab | NSCLC | I/II | 40 | NCT03257722 |
| Copanlisib | Targeting PD-L1 on tumor cells | Nivolumab | Colon cancer | I | 54 | NCT03711058 |

AML: Acute myeloid leukemia; BRAF: B-Raf proto-oncogene; CCA: Cholangiocarcinoma; DNMT: DNA methyltransferase; HDAC: Histone deacetylase; HER2: Human epidermal growth factor receptor 2-positive; HNSCC: Head-and-neck squamous cell carcinoma; HR-MDS: Higher-risk myelodysplastic syndromes; MEK: Mitogen-activated protein kinase kinase; MIBC: Muscle-invasive bladder cancer; NSCLC: Non-small cell lung cancer; PD-1: Programmed cell death protein-1; PDCA: Pancreatic ductal adenocarcinoma; PD-L1: Programmed cell death ligand-1; PI3K: Phosphoinositide 3-kinase; VEGF: Vascular endothelial growth factor.



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