ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2021 September 16; 9(26): 7614-7962

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

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INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
September 16, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

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PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

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https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Cases

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World J Clin Cases 2021 September 16; 9(26): 7643-7652

DOI: 10.12998/wjcc.v9.i26.7643

ISSN 2307-8960 (online)

MINIREVIEWS

Combined targeted therapy and immunotherapy for cancer treatment

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Author contributions: Guo CX and Huang X contributed equally to this work; Guo CX and Huang X contributed to concept and design and manuscript drafting; Xu J, Zhang XZ and Shen YN collected and summarized the relevant research information; Liang TB and Bai XL contributed to the critical manuscript revision; All authors have read and approve the final manuscript.

Supported by The National Key Research and Development Program of China, No. 2019YFC1316000, the National High Technology Research and Development Program of China, No. 2015AA020405, the National Natural Science Foundation of China, No. 81672337; and China Postdoctoral Science Foundation, No. 2020M671761.

Conflict-of-interest statement: The authors declare no potential conflicts of interest.

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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

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.

Citation: Guo CX, Huang X, Xu J, Zhang XZ, Shen YN, Liang TB, Bai XL. Combined targeted therapy and immunotherapy for cancer treatment. *World J Clin Cases* 2021; 9(26): 7643-7652

Manuscript source: Invited manuscript

Specialty type: Medicine, research and experimental

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: June 8, 2021
Peer-review started: June 8, 2021
First decision: June 30, 2021
Revised: July 9, 2021
Accepted: July 28, 2021
Article in press: July 28, 2021
Published online: September 16, 2021

P-Reviewer: Kida YS, Wang CR
S-Editor: Yan JP
L-Editor: Filipodia
P-Editor: Yuan YY

URL: https://www.wjgnet.com/2307-8960/full/v9/i26/7643.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i26.7643

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

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	Targeting PD-L1 on tumor cells	Atezolizumab	Melanoma	II	30	NCT03554083
	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	Targeting PD-L1 on tumor cells	Atezolizumab	HNSCC	II	110	NCT03818061
	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.

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-oncogene^{V600E} (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 BRAF^{V600E}-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 immunemodulatory 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.

REFERENCES

1 **Hodi FS**, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbé C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; **363**: 711-723 [PMID: 20525992 DOI: 10.1056/NEJMoa1003466]

2 **Topalian SL**, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD,

Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardoll DM, Chen L, Sharfman WH, Anders RA, Taube JM, McMiller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, McDonald D, Kollia GD, Gupta A, Wigginton JM, Sznol M. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; **366**: 2443-2454 [PMID: 22658127 DOI: 10.1056/NEJMoa1200690]

3 **Brahmer JR**, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthy S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012; **366**: 2455-2465 [PMID: 22658128 DOI: 10.1056/NEJMoa1200694]

4 **Carlisle JW**, Ramalingam SS. A banner year for immunotherapy and targeted therapy. *Nat Rev Clin Oncol* 2019; **16**: 79-80 [PMID: 30538305 DOI: 10.1038/s41571-018-0138-4]

5 **Wargo JA**, Cooper ZA, Flaherty KT. Universes collide: combining immunotherapy with targeted therapy for cancer. *Cancer Discov* 2014; **4**: 1377-1386 [PMID: 25395294 DOI: 10.1158/2159-8290.CD-14-0477]

6 **Davies H**, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA. Mutations of the BRAF gene in human cancer. *Nature* 2002; **417**: 949-954 [PMID: 12068308 DOI: 10.1038/nature00766]

7 **Tiacci E**, Trifonov V, Schiavoni G, Holmes A, Kern W, Martelli MP, Pucciarini A, Bigerna B, Pacini R, Wells VA, Sportoletti P, Pettirossi V, Mannucci R, Elliott O, Liso A, Ambrosetti A, Pulsoni A, Forconi F, Trentin L, Semenzato G, Inghirami G, Capponi M, Di Raimondo F, Patti C, Arcaini L, Musto P, Pileri S, Haferlach C, Schnittger S, Pizzolo G, Foà R, Farinelli L, Haferlach T, Pasqualucci L, Rabadan R, Falini B. BRAF mutations in hairy-cell leukemia. *N Engl J Med* 2011; **364**: 2305-2315 [PMID: 21663470 DOI: 10.1056/NEJMoa1014209]

8 **Xing M**. BRAF mutation in thyroid cancer. *Endocr Relat Cancer* 2005; **12**: 245-262 [PMID: 15947100 DOI: 10.1677/erc.1.0978]

9 **Corcoran RB**, Ebi H, Turke AB, Coffee EM, Nishino M, Cogdill AP, Brown RD, Della Pelle P, Dias-Santagata D, Hung KE, Flaherty KT, Piris A, Wargo JA, Settleman J, Mino-Kenudson M, Engelman JA. EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib. *Cancer Discov* 2012; **2**: 227-235 [PMID: 22448344 DOI: 10.1158/2159-8290.CD-11-0341]

10 **Chapman PB**, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M, Hogg D, Lorigan P, Lebbe C, Jouary T, Schadendorf D, Ribas A, O'Day SJ, Sosman JA, Kirkwood JM, Eggermont AM, Dreno B, Nolop K, Li J, Nelson B, Hou J, Lee RJ, Flaherty KT, McArthur GA; BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; **364**: 2507-2516 [PMID: 21639808 DOI: 10.1056/NEJMoa1103782]

11 **Flaherty KT**, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, Hamid O, Schuchter L, Cebon J, Ibrahim N, Kudchadkar R, Burris HA 3rd, Falchook G, Algazi A, Lewis K, Long GV, Puzanov I, Lebowitz P, Singh A, Little S, Sun P, Allred A, Ouellet D, Kim KB, Patel K, Weber J. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med* 2012; **367**: 1694-1703 [PMID: 23020132 DOI: 10.1056/NEJMoa1210093]

12 **Straussman R**, Morikawa T, Shee K, Barzily-Rokni M, Qian ZR, Du J, Davis A, Mongare MM, Gould J, Frederick DT, Cooper ZA, Chapman PB, Solit DB, Ribas A, Lo RS, Flaherty KT, Ogino S, Wargo JA, Golub TR. Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. *Nature* 2012; **487**: 500-504 [PMID: 22763439 DOI: 10.1038/nature11183]

13 **Begley J**, Ribas A. Targeted therapies to improve tumor immunotherapy. *Clin Cancer Res* 2008; **14**: 4385-4391 [PMID: 18628452 DOI: 10.1158/1078-0432.CCR-07-4804]

14 **Tang M**, Diao J, Cattral MS. Molecular mechanisms involved in dendritic cell dysfunction in cancer. *Cell Mol Life Sci* 2017; **74**: 761-776 [PMID: 27491428 DOI: 10.1007/s00018-016-2317-8]

15 **Zitvogel L**, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. *Immunity* 2013; **39**: 74-88 [PMID: 23890065 DOI: 10.1016/j.immuni.2013.06.014]

16 **Hughes PE**, Caenepeel S, Wu LC. Targeted Therapy and Checkpoint Immunotherapy Combinations for the Treatment of Cancer. *Trends Immunol* 2016; **37**: 462-476 [PMID: 27216414 DOI: 10.1016/j.it.2016.04.010]

17 **Newbold A**, Falkenberg KJ, Prince HM, Johnstone RW. How do tumor cells respond to HDAC inhibition? *FEBS J* 2016; **283**: 4032-4046 [PMID: 27112360 DOI: 10.1111/febs.13746]

18 **Zahnow CA**, Topper M, Stone M, Murray-Stewart T, Li H, Baylin SB, Casero RA Jr. Inhibitors of DNA Methylation, Histone Deacetylation, and Histone Demethylation: A Perfect Combination for Cancer Therapy. *Adv Cancer Res* 2016; **130**: 55-111 [PMID: 27037751 DOI: 10.1016/bs.acr.2016.01.007]

19 **Ribas A**, Wolchok JD. Combining cancer immunotherapy and targeted therapy. *Curr Opin Immunol* 2013; **25**: 291-296 [PMID: 23561594 DOI: 10.1016/j.coi.2013.02.011]

20 **West AC**, Smyth MJ, Johnstone RW. The anticancer effects of HDAC inhibitors require the immune system. *Oncoimmunology* 2014; **3**: e27414 [PMID: 24701376 DOI: 10.4161/onci.27414]

21 **Setiadi AF**, Omilusik K, David MD, Seipp RP, Hartikainen J, Gopaul R, Choi KB, Jefferies WA. Epigenetic enhancement of antigen processing and presentation promotes immune recognition of tumors. *Cancer Res* 2008; **68**: 9601-9607 [PMID: 19047136 DOI: 10.1158/0008-5472.CAN-07-5270]

22 **Kato Y**, Yoshimura K, Shin T, Verheul H, Hammers H, Sanni TB, Salumbides BC, Van Erp K, Schulick R, Pili R. Synergistic *in vivo* antitumor effect of the histone deacetylase inhibitor MS-275 in combination with interleukin 2 in a murine model of renal cell carcinoma. *Clin Cancer Res* 2007; **13**: 4538-4546 [PMID: 17671140 DOI: 10.1158/1078-0432.CCR-07-0014]

23 **Kim K**, Skora AD, Li Z, Liu Q, Tam AJ, Blosser RL, Diaz LA Jr, Papadopoulos N, Kinzler KW, Vogelstein B, Zhou S. Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells. *Proc Natl Acad Sci USA* 2014; **111**: 11774-11779 [PMID: 25071169 DOI: 10.1073/pnas.1410626111]

24 **Vo DD**, Prins RM, Begley JL, Donahue TR, Morris LF, Bruhn KW, de la Rocha P, Yang MY, Mok S, Garban HJ, Craft N, Economou JS, Marincola FM, Wang E, Ribas A. Enhanced antitumor activity induced by adoptive T-cell transfer and adjunctive use of the histone deacetylase inhibitor LAQ824. *Cancer Res* 2009; **69**: 8693-8699 [PMID: 19861533 DOI: 10.1158/0008-5472.CAN-09-1456]

25 **Christiansen AJ**, West A, Banks KM, Haynes NM, Teng MW, Smyth MJ, Johnstone RW. Eradication of solid tumors using histone deacetylase inhibitors combined with immune-stimulating antibodies. *Proc Natl Acad Sci USA* 2011; **108**: 4141-4146 [PMID: 21368108 DOI: 10.1073/pnas.1011037108]

26 **Sumimoto H**, Imabayashi F, Iwata T, Kawakami Y. The BRAF-MAPK signaling pathway is essential for cancer-immune evasion in human melanoma cells. *J Exp Med* 2006; **203**: 1651-1656 [PMID: 16801397 DOI: 10.1084/jem.20051848]

27 **Kono M**, Dunn IS, Durda PJ, Butera D, Rose LB, Haggerty TJ, Benson EM, Kurnick JT. Role of the mitogen-activated protein kinase signaling pathway in the regulation of human melanocytic antigen expression. *Mol Cancer Res* 2006; **4**: 779-792 [PMID: 17050671 DOI: 10.1158/1541-7786.MCR-06-0077]

28 **Boni A**, Cogdill AP, Dang P, Udayakumar D, Njauw CN, Sloss CM, Ferrone CR, Flaherty KT, Lawrence DP, Fisher DE, Tsao H, Wargo JA. Selective BRAFV600E inhibition enhances T-cell recognition of melanoma without affecting lymphocyte function. *Cancer Res* 2010; **70**: 5213-5219 [PMID: 20551059 DOI: 10.1158/0008-5472.CAN-10-0118]

29 **Ebert PJR**, Cheung J, Yang Y, McNamara E, Hong R, Moskalenko M, Gould SE, Maecker H, Irving BA, Kim JM, Belvin M, Mellman I. MAP Kinase Inhibition Promotes T Cell and Anti-tumor Activity in Combination with PD-L1 Checkpoint Blockade. *Immunity* 2016; **44**: 609-621 [PMID: 26944201 DOI: 10.1016/j.immuni.2016.01.024]

30 **Koya RC**, Mok S, Otte N, Blacketor KJ, Comin-Anduix B, Tumeh PC, Minasyan A, Graham NA, Graeber TG, Chodon T, Ribas A. BRAF inhibitor vemurafenib improves the antitumor activity of adoptive cell immunotherapy. *Cancer Res* 2012; **72**: 3928-3937 [PMID: 22693252 DOI: 10.1158/0008-5472.CAN-11-2837]

31 **Cooper ZA**, Frederick DT, Ahmed Z, Wargo JA. Combining checkpoint inhibitors and BRAF-targeted agents against metastatic melanoma. *Oncoimmunology* 2013; **2**: e24320 [PMID: 23762807 DOI: 10.4161/onci.24320]

32 **Frederick DT**, Piris A, Cogdill AP, Cooper ZA, Lezcano C, Ferrone CR, Mitra D, Boni A, Newton LP, Liu C, Peng W, Sullivan RJ, Lawrence DP, Hodi FS, Overwijk WW, Lizée G, Murphy GF, Hwu P, Flaherty KT, Fisher DE, Wargo JA. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. *Clin Cancer Res* 2013; **19**: 1225-1231 [PMID: 23307859 DOI: 10.1158/1078-0432.CCR-12-1630]

33 **Ellis LM**, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. *Nat Rev Cancer* 2008; **8**: 579-591 [PMID: 18596824 DOI: 10.1038/nrc2403]

34 **Peske JD**, Woods AB, Engelhard VH. Control of CD8 T-Cell Infiltration into Tumors by Vasculature and Microenvironment. *Adv Cancer Res* 2015; **128**: 263-307 [PMID: 26216636 DOI: 10.1016/bs.acr.2015.05.001]

35 **Alfaro C**, Suarez N, Gonzalez A, Solano S, Erro L, Dubrot J, Palazon A, Hervas-Stubbs S, Gurpide A, Lopez-Picazo JM, Grande-Pulido E, Melero I, Perez-Gracia JL. Influence of bevacizumab, sunitinib and sorafenib as single agents or in combination on the inhibitory effects of VEGF on human dendritic cell differentiation from monocytes. *Br J Cancer* 2009; **100**: 1111-1119 [PMID: 19277038 DOI: 10.1038/sj.bjc.6604965]

36 **Voron T**, Colussi O, Marcheteau E, Pernot S, Nizard M, Pointet AL, Latreche S, Bergaya S, Benhamouda N, Tanchot C, Stockmann C, Combe P, Berger A, Zinzindohoue F, Yagita H, Tartour E, Taieb J, Terme M. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. *J Exp Med* 2015; **212**: 139-148 [PMID: 25601652 DOI: 10.1084/jem.20140559]

37 **Huang Y**, Yuan J, Righi E, Kamoun WS, Ancukiewicz M, Nezivar J, Santosuosso M, Martin JD, Martin MR, Vianello F, Leblanc P, Munn LL, Huang P, Duda DG, Fukumura D, Jain RK, Poznansky MC. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. *Proc Natl Acad Sci USA* 2012; **109**: 17561-17566 [PMID: 23045683 DOI: 10.1073/pnas.1215397109]

38 **Shrimali RK**, Yu Z, Theoret MR, Chinnasamy D, Restifo NP, Rosenberg SA. Antiangiogenic agents

can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. *Cancer Res* 2010; **70**: 6171-6180 [PMID: 20631075 DOI: 10.1158/0008-5472.CAN-10-0153]

39 **Rini BI**, Weinberg V, Fong L, Conry S, Hershberg RM, Small EJ. Combination immunotherapy with prostatic acid phosphatase pulsed antigen-presenting cells (provenge) plus bevacizumab in patients with serologic progression of prostate cancer after definitive local therapy. *Cancer* 2006; **107**: 67-74 [PMID: 16736512 DOI: 10.1002/cncr.21956]

40 **Hodi FS**, Lawrence D, Lezcano C, Wu X, Zhou J, Sasada T, Zeng W, Giobbie-Hurder A, Atkins MB, Ibrahim N, Friedlander P, Flaherty KT, Murphy GF, Rodig S, Velazquez EF, Mihm MC Jr, Russell S, DiPiro PJ, Yap JT, Ramaiya N, Van den Abbeele AD, Gargano M, McDermott D. Bevacizumab plus ipilimumab in patients with metastatic melanoma. *Cancer Immunol Res* 2014; **2**: 632-642 [PMID: 24838938 DOI: 10.1158/2326-6066.CIR-14-0053]

41 **Pollizzi KN**, Powell JD. Regulation of T cells by mTOR: the known knowns and the known unknowns. *Trends Immunol* 2015; **36**: 13-20 [PMID: 25522665 DOI: 10.1016/j.it.2014.11.005]

42 **Peng W**, Chen JQ, Liu C, Malu S, Creasy C, Tetzlaff MT, Xu C, McKenzie JA, Zhang C, Liang X, Williams LJ, Deng W, Chen G, Mbofung R, Lazar AJ, Torres-Cabala CA, Cooper ZA, Chen PL, Tieu TN, Spranger S, Yu X, Bernatchez C, Forget MA, Haymaker C, Amaria R, McQuade JL, Glitza IC, Cascone T, Li HS, Kwong LN, Heffernan TP, Hu J, Bassett RL Jr, Bosenberg MW, Woodman SE, Overwijk WW, Lizée G, Roszik J, Gajewski TF, Wargo JA, Gershenwald JE, Radvanyi L, Davies MA, Hwu P. Loss of PTEN Promotes Resistance to T Cell-Mediated Immunotherapy. *Cancer Discov* 2016; **6**: 202-216 [PMID: 26645196 DOI: 10.1158/2159-8290.CD-15-0283]

43 **Parsa AT**, Waldron JS, Panner A, Crane CA, Parney IF, Barry JJ, Cachola KE, Murray JC, Tihan T, Jensen MC, Mischel PS, Stokoe D, Pieper RO. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. *Nat Med* 2007; **13**: 84-88 [PMID: 17159987 DOI: 10.1038/nm1517]

44 **Ali K**, Soond DR, Pineiro R, Hagemann T, Pearce W, Lim EL, Bouabe H, Scudamore CL, Hancox T, Maecker H, Friedman L, Turner M, Okkenhaug K, Vanhaesebroeck B. Inactivation of PI(3)K p110δ breaks regulatory T-cell-mediated immune tolerance to cancer. *Nature* 2014; **510**: 407-411 [PMID: 24919154 DOI: 10.1038/nature13444]

45 **Furman RR**, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, Barrientos JC, Zelenetz AD, Kipps TJ, Flinn I, Ghia P, Eradat H, Ervin T, Lamanna N, Coiffier B, Pettitt AR, Ma S, Stilgenbauer S, Cramer P, Aiello M, Johnson DM, Miller LL, Li D, Jahn TM, Dansey RD, Hallek M, O'Brien SM. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2014; **370**: 997-1007 [PMID: 24450857 DOI: 10.1056/NEJMoa1315226]

46 **Gopal AK**, Kahl BS, de Vos S, Wagner-Johnston ND, Schuster SJ, Jurczak WJ, Flinn IW, Flowers CR, Martin P, Viardot A, Blum KA, Goy AH, Davies AJ, Zinzani PL, Dreyling M, Johnson D, Miller LL, Holes L, Li D, Dansey RD, Godfrey WR, Salles GA. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med* 2014; **370**: 1008-1018 [PMID: 24450858 DOI: 10.1056/NEJMoa1314583]

47 **Araki K**, Turner AP, Shaffer VO, Gangappa S, Keller SA, Bachmann MF, Larsen CP, Ahmed R. mTOR regulates memory CD8 T-cell differentiation. *Nature* 2009; **460**: 108-112 [PMID: 19543266 DOI: 10.1038/nature08155]

48 **Rao RR**, Li Q, Odunsi K, Shrikant PA. The mTOR kinase determines effector *vs* memory CD8+ T cell fate by regulating the expression of transcription factors T-bet and Eomesodermin. *Immunity* 2010; **32**: 67-78 [PMID: 20060330 DOI: 10.1016/j.immuni.2009.10.010]

49 **Li Q**, Rao RR, Araki K, Pollizzi K, Odunsi K, Powell JD, Shrikant PA. A central role for mTOR kinase in homeostatic proliferation induced CD8+ T cell memory and tumor immunity. *Immunity* 2011; **34**: 541-553 [PMID: 21511183 DOI: 10.1016/j.immuni.2011.04.006]

50 **Wang Y**, Wang XY, Subjeck JR, Shrikant PA, Kim HL. Temsirolimus, an mTOR inhibitor, enhances anti-tumour effects of heat shock protein cancer vaccines. *Br J Cancer* 2011; **104**: 643-652 [PMID: 21285988 DOI: 10.1038/bjc.2011.15]

51 **Jiang Q**, Weiss JM, Back T, Chan T, Ortaldo JR, Guichard S, Wiltrout RH. mTOR kinase inhibitor AZD8055 enhances the immunotherapeutic activity of an agonist CD40 antibody in cancer treatment. *Cancer Res* 2011; **71**: 4074-4084 [PMID: 21540234 DOI: 10.1158/0008-5472.CAN-10-3968]

52 **Ribas A**, Hodi FS, Callahan M, Konto C, Wolchok J. Hepatotoxicity with combination of vemurafenib and ipilimumab. *N Engl J Med* 2013; **368**: 1365-1366 [PMID: 23550685 DOI: 10.1056/NEJMc1302338]

53 **Jafari S**, Molavi O, Kahroba H, Hejazi MS, Maleki-Dizaji N, Barghi S, Kiaie SH, Jadidi-Niaragh F. Clinical application of immune checkpoints in targeted immunotherapy of prostate cancer. *Cell Mol Life Sci* 2020; **77**: 3693-3710 [PMID: 32006051 DOI: 10.1007/s00018-020-03459-1]

54 **Ackerman A**, Klein O, McDermott DF, Wang W, Ibrahim N, Lawrence DP, Gunturi A, Flaherty KT, Hodi FS, Kefford R, Menzies AM, Atkins MB, Long GV, Sullivan RJ. Outcomes of patients with metastatic melanoma treated with immunotherapy prior to or after BRAF inhibitors. *Cancer* 2014; **120**: 1695-1701 [PMID: 24577748 DOI: 10.1002/cncr.28620]

55 **Wang Y**, Camirand G, Lin Y, Froicu M, Deng S, Shlomchik WD, Lakkis FG, Rothstein DM. Regulatory T cells require mammalian target of rapamycin signaling to maintain both homeostasis and alloantigen-driven proliferation in lymphocyte-replete mice. *J Immunol* 2011; **186**: 2809-2818 [PMID: 21270412 DOI: 10.4049/jimmunol.0903805]

56 **Procaccini C**, De Rosa V, Galgani M, Abanni L, Calì G, Porcellini A, Carbone F, Fontana S, Horvath

TL, La Cava A, Matarese G. An oscillatory switch in mTOR kinase activity sets regulatory T cell responsiveness. *Immunity* 2010; **33**: 929-941 [PMID: 21145759 DOI: 10.1016/j.immuni.2010.11.024]

57 **Mannick JB**, Del Giudice G, Lattanzi M, Valiante NM, Praestgaard J, Huang B, Lonetto MA, Maecker HT, Kovarik J, Carson S, Glass DJ, Klickstein LB. mTOR inhibition improves immune function in the elderly. *Sci Transl Med* 2014; **6**: 268ra179 [PMID: 25540326 DOI: 10.1126/scitranslmed.3009892]

58 **Chiou VL**, Burotto M. Pseudoprogression and Immune-Related Response in Solid Tumors. *J Clin Oncol* 2015; **33**: 3541-3543 [PMID: 26261262 DOI: 10.1200/JCO.2015.61.6870]

59 **Di Giacomo AM**, Danielli R, Guidoboni M, Calabrò L, Carlucci D, Miracco C, Volterrani L, Mazzei MA, Biagioli M, Altomonte M, Maio M. Therapeutic efficacy of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with metastatic melanoma unresponsive to prior systemic treatments: clinical and immunological evidence from three patient cases. *Cancer Immunol Immunother* 2009; **58**: 1297-1306 [PMID: 19139884 DOI: 10.1007/s00262-008-0642-y]

60 **Wolchok JD**, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009; **15**: 7412-7420 [PMID: 19934295 DOI: 10.1158/1078-0432.CCR-09-1624]

61 **Sznol M**. Combination Strategies PD-1/PD-L1 Antagonists. *Cancer J* 2018; **24**: 54-57 [PMID: 29360729 DOI: 10.1097/PPO.0000000000000304]

62 **Twyman-Saint Victor C**, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, Benci JL, Xu B, Dada H, Odorizzi PM, Herati RS, Mansfield KD, Patsch D, Amaravadi RK, Schuchter LM, Ishwaran H, Mick R, Pryma DA, Xu X, Feldman MD, Gangadhar TC, Hahn SM, Wherry EJ, Vonderheide RH, Minn AJ. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature* 2015; **520**: 373-377 [PMID: 25754329 DOI: 10.1038/nature14292]

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