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CURRENT LANDSCAPE FROM CLINICAL TRIALS AND FUTURE OF COMBINED CHECKPOINTS BLOCKADE IMMUNOTHERAPY IN CANCERS

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ABSTRACT: Immunotherapy is among cancer immunology's fastest and most furious treatment strategies. The therapeutic perspective of checkpoint inhibitors is represented through the Food and Drug Administration (FDA) approvals for their implementation in various malignancies. Efforts to improve results with immunotherapeutic agents have led to the design of advanced treatment strategies. Current pre-clinical evidence estimating immune checkpoint inhibitors in several cancer cell lines has recommended that combinatorial approaches may have better survival results than monotherapy. Experimental trials evaluating combined therapy with anti-PD-1/ PD-L1 plus anti-CTLA-4 checkpoint inhibitors have reported considerable leads in survival indices over single immunotherapy. The therapeutic prospective of combinatorial approaches is focused on nivolumab with ipilimumab for advanced melanoma patients. Combined checkpoint inhibition with anti-PD-1/PD-L1 plus anti-CTLA-4 monoclonal antibodies is being estimated for broadly cancer histological studies.

INTRODUCTION: The regulation of immune responses by monoclonal antibodies is a ground-breaking therapeutic alternative strategy in cancer biology. Over the years, several immunotherapeutics have received approval through the FDA as standard care treatment for various malignancies. However, with increasing experience in using immunotherapy agents in clinical settings, several limitations, like treatment resistance and undesirable immunogenicity [1]. Extensive efforts have been made toward testing novel immune checkpoints, which are expected to be an option for the next generation of immunotherapy agents.

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The basic objective in advancing cancer immunotherapy is to better improvement in medical outcomes. The implement of combined checkpoint blockade inhibitor is being applied to achieve this objective. This approach intends to exploit the distinct mechanisms of immuno-modulation of two monoclonal antibodies in a single treatment regimen [2]. The combined use of an anti-CTLA-4 immune checkpoint inhibitor with an anti-PD-1/PD-L1 monoclonal antibodies combination therapy may have complementary action, since yielding a higher clinical efficiency than either agent individually.

Presently, combination checkpoint inhibition is being extensively evaluated for potential medical benefit in a large number of tumor histological studies [3]. Because of positive outcomes in preliminary trials, nivolumab (IgG_4 anti-PD-1 Mab) with ipilimumab (IgG_1 anti-CTLA-4 Mab) is one of the most enthusiastically investigated combined

immunotherapy regimens, with over 100 clinical trials in various stages [4]. Additionally, other PD-1/PD-L1 inhibitors with CTLA-4 inhibitor combination checkpoint inhibition regimens that are currently in clinical trials involve atezolizumab (anti-PD-L1 Mab) plus ipilimumab, pembrolizumab (IgG_4 anti-PD-1 Mab) plus ipilimumab, and tremelimumab (IgG_2 anti-CTLA-4 Mab) plus durvalumab (Fc optimized anti-PD-L1 Mab) [5].

Role of CTLA-4 Immune Checkpoint in Anticancer Mechanism: The process of T-cell activation mainly requires two signals. The first signal comes from the binding of the T-cell receptor (TCR) to the major histocompatibility complex (MHC) molecule introduced through an antigen-presenting cell (APC).

The costimulatory signal may arise from one of several distinct T-cells with APC interactions. One such pathway is the involvement of CD28 on T-cells with CD80 (B7-1) or CD86 (B7-2) on APCs **Fig. 1**. T-cell activity can be modulated by regulating costimulatory signal generation by various mechanisms [6].

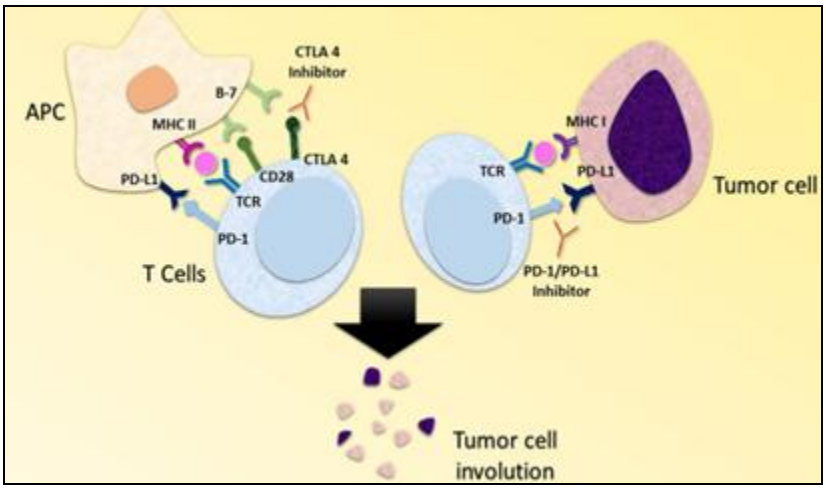

FIG. 1: MECHANISM OF CTLA-4 AND PD-1/PD-L1 INHIBITION

Various signaling pathways have been involved in the modulation of T-cell activity. The CTLA-4 molecule is a homolog of CD28 expressed by T-cells **Fig. 1**. The impact of CTLA-4 on T-cell activity primarily focuses to priming phase of T-cell activation. CTLA-4 competitively binds to B7 on APCs and inhibits the costimulatory signal that arises from the engagement of CD28 with B7, so diminishing the T-cell immune response. The upregulation of CTLA-4 expression on $CD8^+$ and $CD4^+$ T-cells precludes stimulatory signaling from binding together CD28-B7 and TCR-MHC. Beside of this, regulatory T-cells (Treg cells) exhibit constitutive expression of CTLA-4 [7].

Role of PD-1/PD-L1 Immune Checkpoint in Anticancer Mechanism: The PD-1 molecule is akin to CTLA-4, which is a member of the B7-CD28 family and is expressed by myeloid-derived cells, B-cells, and T-cells. PD-1 has two complementary ligands, mainly PD-L1 and PD-L2. PD-L1 is expressed by diverse cells, including hematopoietic cells, leucocytes, and cancer cells, whereas PD-L2 is expressed by dendritic cells and macrophages [8]. The PD-1 receptor on T-cells binds PD-L1 expressed by APCs and restricts pro-inflammatory actions like T-cell proliferation and cytokine production **Fig. 1**.

Furthermore, current proof has indicated that PD-1/PD-L1 interactions clear the way for immune escape by cancer cells. This phenomenon has been assigned to PD-1/PD-L1 mediated induction of anergy and apoptosis of activated T-cells, tumor resistance to cytotoxic T-cell response, and differentiation of $CD4^+$ T-cells into $FoxP3^+$ $CD4^+$ regulatory T-cells [9]. The detailed knowledge of various pathways regulating T-cell and APC interactions has been midway to identifying the points of interference that allow us to balance host immune responses. The foregoing evidence and other studies with similar results elicited the development of PD-1/PD-L1 and CTLA-4 checkpoint inhibitors for potential use in anti-cancer therapy [10].

Rational for Combined Immune Checkpoint Therapy: Combine immunotherapy, including PD-1/PD-L1 with CTLA-4 checkpoint blockade inhibitors, has been studied in various cancer cell lines. For instance, in murine models experiment, vaccination with B16-Flt-3 ligand (Fvax) ahead with CTLA-4 antibody promoted 10 % cancer rejection in mice with pre-implanted B16-BL6 melanoma. Fvax with PD-1 blockade showed 25 % cancer rejection in mice, whereas combined use of CTLA-4 and PD-1 checkpoint blockade inhibitors followed 50 % rejection of B16-BL6 melanoma [11]. On the addition of a PD-L1 inhibitor to the above, the test animals exhibited rejection of melanoma is 65 %. The outcomes observed with combined PD-1 and CTLA-4 blockade were found to correlate with an increase in effector $CD4^+$ T -cell to regulatory T-cell (Treg) ratio as well as $CD8^+$ T-cell to Treg cell ratio in cancerous tissue [12].

Another notable observation was that a high percentage of T-cells positive for CTLA-4 and PD-1 that would have undergone anergy remained active with combined blockade. Combination therapy, dual checkpoint inhibition CTLA-4 with PD-1 blockade was associated with a greater enhancement in tumor induced lymphocyte (TIL) activity and proliferation similar to CTLA-4 or PD-1 blockade alone, while decreased the number and concurrently blunted the functional markers of activated Treg cells [13]. Combined immune checkpoint blockade decreases suppression of the host immune system, whilst promoting inflammation in the tumor microenvironment. Moreover, the vast amount of preclinical data also suggested that the anti-cancer activity of combination therapy with CTLA-4 plus PD-1/PD-L1 checkpoint inhibitors may have superior outcomes compared to CTLA-4 or PD-1 monotherapy [14].

Emergence of Combined Immune Checkpoint Therapy: Cancer immunosurveillance considered one of the primary natural defensive mechanisms against aberrant cell populations. While immune cells recognize and eliminate transformed cells through various cellular interactions, the immune system also shapes cancer immunogenicity (immunoediting). However, cancer cells gradually undergo immune selection, disrupting the equilibrium with immune cells, consequently generating a cancer cell population that effectively evades immune surveillance [15]. While alterations in the tumor microenvironment mediate immune escape, therapeutic agents that can restore immune surveillance or prevent the immune escape of cancer cell populations could potentially significantly impact clinical oncology. Immunogenic cell death inducers, immunostimulatory cytokines, pattern recognition receptors, and cancer-targeting antibodies have exploited cancer patients [16].

Numerous immunotherapeutic drugs have received FDA approval for use as monotherapy in a variety of cancer histological studies. For instance, nivolumab has been approved for patients with melanoma, renal cell carcinoma, metastatic squamous cell carcinoma (MSCC), Hodgkin's lymphoma (HL) and advanced lung cancer. Moreover, Pembrolizumab, another anti-PD-1 Mab, is approved for use in patients with MSCC and melanoma. Likewise, atezolizumab is approved for patients with urothelial carcinoma [17]. Current clinical data comparing combined therapy with nivolumab and ipilimumab vs ipilimumab monotherapy in treatment melanoma patients withdrew much noticeable. In patients with BRAF-wild type melanoma, the investigators reported an objective response of 61 % instead of 11 % with combined checkpoint inhibition and ipilimumab monotherapy, respectively [18].

Furthermore, 22 % of participants who received combined therapy revealed a complete response compared to none who received ipilimumab monotherapy alone. Combined therapy with nivolumab and ipilimumab in melanoma patients became the first FDA-approved checkpoint inhibition drugs [19]. This prompted comprehensive efforts to explore the application of combined immunotherapy with anti-PD-1/PD-L1 and anti-CTLA-4 Mabs for patients with different malignancies. While many clinical trials currently evaluate several PD-1/PD-L1 plus CTLA-4 checkpoint inhibitor, positive outcomes in preliminary trials have made way for more intensive efforts to explore the full potential of combination regimens [20].

Clinical Trials: Current Landscape and Investigation: The United States National

Institutes of Health lists a total of 44 ongoing clinical trials (clinicaltrials.gov) estimating combination immunotherapy with anti-PD-1/ PD-L1 with anti-CTLA-4 antibodies for patients with melanoma **Fig. 2**. The assigned combination therapy regimens involve nivolumab plus ipilimumab, pembrolizumab plus ipilimumab, and atezolizumab plus ipilimumab, and durvalumab vice-versa **Fig. 3**. A many of these clinical trials focus on survival and other treatment response indices, while a limited number of trials are investigating the safety profile and maximum tolerable dose (MTD) of combined immunotherapy protocols [21].

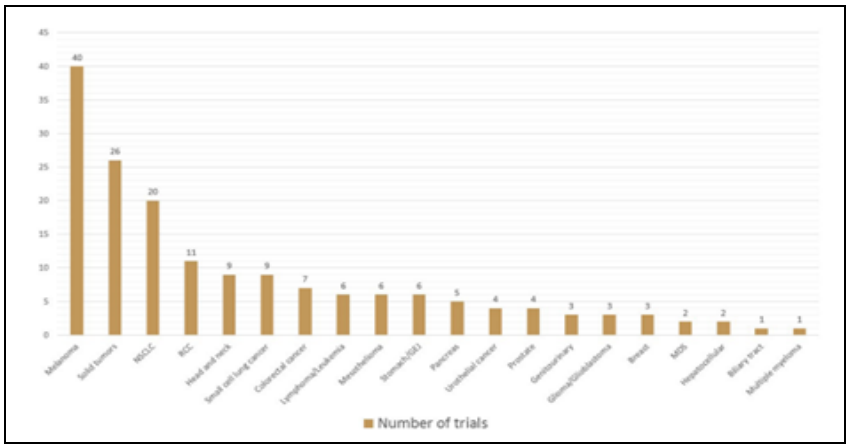

FIG. 2: NUMBER OF COMBINED CHECKPOINT INHIBITION TRIALS FOR VARIOUS CANCER HISTOLOGICAL STUDIES [ABBREVIATIONS: NSCLC (NON-SMALL CELL LUNG CARCINOMA), RCC (RENAL CELL CARCINOMA), GEJ (GASTRO-ESOPHAGEAL JUNCTION), MDS (MYELODYSPLASTIC SYNDROME)]

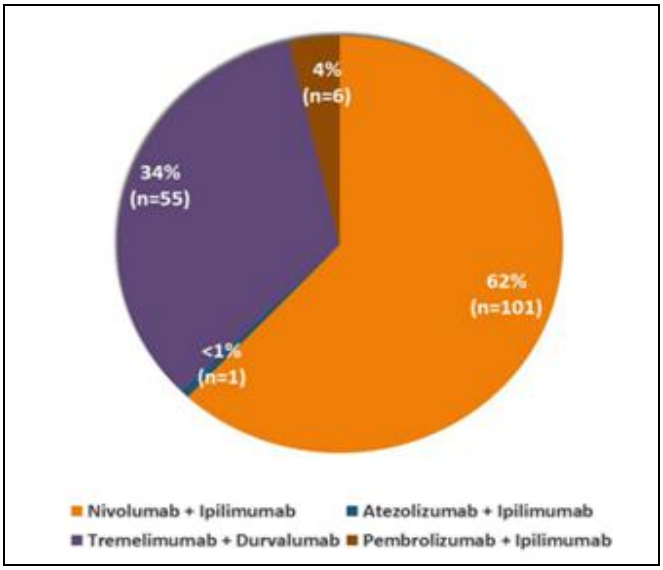

FIG. 3: RELATIVE NUMBER OF CLINICAL TRIALS FOR 4 COMBINATIONS OF IMMUNOTHERAPEUTIC AGENTS

Combined Checkpoint Inhibition in Melanoma: Currently, only one trial is in the process towards dual checkpoint inhibition with anti-PD-1/PD-L1 plus anti-CTLA-4 Mabs in patients with melanoma of recruiting participants that will receive ipilimumab with pembrolizumab. Approximately two-third of all ongoing trials in melanoma patients are investigating combined therapy with nivolumab plus ipilimumab. Several different methodologies for using nivolumab and ipilimumab have been identified and are presently being investigated for potential clinical benefit in two trials [22].

One trial will compare the incidence of adverse events, overall response rate, and progression-free survival with concurrent versus sequential administration of nivolumab and ipilimumab in the induction phase. In another trial, Check Mate 064, will evaluate the response duration, response rate, progression rate and study proportion of participants that develop grade 3-5 adverse events when using nivolumab earlier to ipilimumab versus ipilimumab earlier to nivolumab in the induction phase. Treatment protocols in five trials include using nivolumab and ipilimumab with supplementary anticancer agents [23].

Another trial will explore the clinical efficiency and incidence of adverse events for nivolumab plus TAK580, nivolumab, and plozalizumab, and the combined use of nivolumab plus ipilimumab and vedolizumab, each in separate arms. Similarly, a different trial will evaluate the safety profile and clinical efficacy with a combination dabrafenib and

trametinib in the induction phase, followed by ipilimumab or nivolumab [24]. Lastly, one trial will analyze response to vemurafenib plus cobimetinib in the induction phase followed by nivolumab plus ipilimumab, versus nivolumab plus ipilimumab combination therapy alone. Some additional treatment modalities with nivolumab plus ipilimumab combined therapy for melanoma is being scrutinized in three trials [25].

Combined Checkpoint Inhibition in NSCLC: Combination therapy with anti-PD-1/PD-L1 and anti-CTLA-4 antibodies in patients with NSCLC (Non-small cell lung cancer) is presently being explored in 16 ongoing trials. Over half (10/16 trials) of these trials are estimating combined therapy with nivolumab and ipilimumab with or without other therapeutic modalities. Other combined checkpoint inhibition regimens being scrutinized in patients with NSCLC involve tremelimumab plus durvalumab (5/16 trials) and pembrolizumab plus ipilimumab (1/16 trials) [26].

Currently, five ongoing trials are evaluating with combined use of anti-PD-1/PD-L1 and anti-CTLA-4 Mabs with various chemotherapeutic agents. Particular trials described treatment cohorts based on patient cancer marker status. Patients with EGFR mutant NSCLC will receive erlotinib with either nivolumab or ipilimumab and those with ALK repositioned NSCLC will be managed crizotinib with either nivolumab or ipilimumab [27].

Another trial will compare PFS, ORR, and response duration in patients with advanced NSCLC after delivering of dasatinib plus nivolumab, BMS-986016 (anti-LAG-3 Mab) plus nivolumab and ipilimumab plus nivolumab.

Participants applied in Check Mate 227 will be recombined to receive nivolumab plus platinum couplet chemotherapy or combined therapy with nivolumab plus ipilimumab. Likewise, Check Mate 722 will estimate PFS for T790 M negative, EGFR mutant NSCLC patients treated with nivolumab plus platinum couplet chemotherapy (cisplatin plus pemetrexed) and ipilimumab plus nivolumab combined therapy [28]. This trial will also estimate the combined use of pembrolizumab with one/more standard chemotherapeutic agents using pre-described treatment protocols. These involve carboplatin, pemetrexed, paclitaxel, bevacizumab, erlotinib, and gefitinib. The progress of a treatment regimen that integrates immunotherapy with PD-1/PD-L1 and CTLA-4 immune checkpoint inhibitors with surgery or radiation therapy has been approachable in one trial [29].

This trial will determine the RP2D for four combined therapies in NSCLC patients with brain metastases at the accession time. The treatment regimens identified by the study protocol involve nivolumab with stereotactic radiosurgery, nivolumab plus ipilimumab with whole-brain radiation therapy, nivolumab plus whole-brain radiation therapy, and nivolumab plus ipilimumab with stereotactic radiosurgery [30].

Data on safety and survival benefit from combination therapy with PD-1/PD-L1 and CTLA-4 checkpoint inhibitors in NSCLC are available from 3 trials. A single trial estimated four experimental dosing schedules of combination immunotherapy with nivolumab and ipilimumab to one monotherapy in order to visualize the regimen that entrances maximum clinical benefit with an allowable adverse-effects data [31].

RESULTS AND DISCUSSION: Significant passion surrounding combined immunotherapy with PD-1/PD-L1 and CTLA-4 checkpoint inhibitors. The superior results with combined immunotherapy over single-agent regimens in preclinical studies, with the approval of nivolumab plus ipilimumab combination therapy for patients with melanoma have shed light on the therapeutic potential [32].

The possibility of expanding the spectrum of indications for combination checkpoint inhibition to a broad range of cancer histology is being explored in various trials. Concurrently, extensive efforts have been scrutinized to improve clinical benefit to adverse effects ratios with combination checkpoint inhibition [33].

Combined therapy with anti-PD-1/PD-L1 and anti-CTLA-4 in advanced melanoma has shown better survival results in comparison with monotherapy **Fig. 4**.

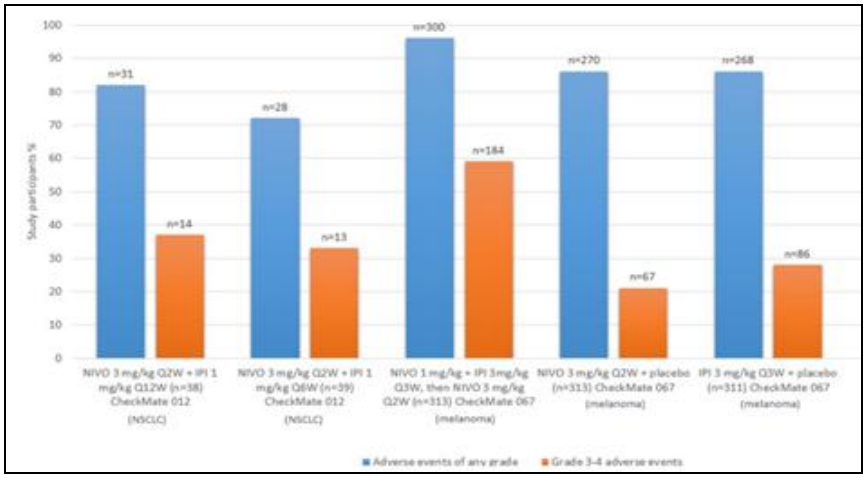

FIG. 4: COMPARISON OF OBJECTIVE RESPONSE IN SELECTIVE PATIENTS TRAILS WITH DIFFERENT TREATMENT REGIMENS (CHECK MATE 012, NCT02000947 AND CHECK MATE 067) [ABBREVIATIONS: NIVO (NIVOLUMAB), IPI (IPILIMUMAB), DURVA (DURVALUMAB), TREME (TREMELIMUMAB), Q(N)W (EVERY (N) WEEKS), NSCLC (NON-SMALL CELL LUNG CANCER)]

Several outcomes have tried to tally the PD-L1 expression response to combined checkpoints inhibition with anti-PD-1/PD-L1 plus anti-CTLA-4 antibodies. PD-L1 positivity has classically been defined as visualization of at least 5% of cancer cells with PD-L1 staining in a section containing a minimum of 100 cells suitable for evaluation [34].

Practical approach for selecting the most suitable immunotherapy command (monotherapy vs. combined therapy) may be through creative treatment data including cancer PD-L1 status. Treatment-related adverse incidents with combined checkpoint inhibition have been a concerning matter in critical trials [35]. The Check Mate 069 trial estimated combined immunotherapy with nivolumab and ipilimumab vs. ipilimumab monotherapy in melanoma patients, resulted treatment associated grade 3-4 adverse circumstances in receiving combined therapy (54 %) as compared to monotherapy (24 %) [36].

These outcomes conclude that melanoma patients receiving combined checkpoint inhibition developed more severe drug-related adverse events than treatment with monotherapy. Although 68 % of patients that discontinued combination therapy due to toxicity exhibited an objective response, concerns over treatment-related toxicity with combination checkpoint inhibition regimens persuade some to favor immune checkpoint inhibitor monotherapy. In order to validate these findings, the same combination therapy regimen was evaluated in the Check Mate 067 trial and compared ipilimumab monotherapy and nivolumab monotherapy in parallel arms [37]. The frequency of grade 3-4 adverse events in patients treated with combination therapy (59 % patients) was higher than that recorded for patients receiving monotherapy with ipilimumab (28 % patients) or nivolumab (21 % patients).

Although treatment-related adverse events with combined therapy were reported and concluded as feasible, this regimen was preferable for further studies. Moreover, one should be cautious in selection of combined checkpoint immunotherapy over monotherapy in older patients with high fragility index [38].

A retroactive pooled analysis directed to study the efficiency and safety of combined immunotherapy with nivolumab and ipilimumab in patients that discontinued therapy because of adverse circumstances presented interesting findings. Current studies have recommended that sequential direction of immune checkpoint inhibitors targeting different pathways may benefit cancer patients revealing treatment resistance [39].

A multi-center retroactive study estimated results with ipilimumab and combined therapy with nivolumab and ipilimumab in advanced melanoma patients that previously failed treatment with anti-PD-1 antibodies. Patients receiving ipilimumab monotherapy were scrutinized to have better disease control as compared to those receiving

combined immune checkpoint inhibition (42 % vs 33 %) [40].

CONCLUSION: Combined immunotherapy is evolving at a magnificent footstep. In view of initial success in melanoma patients, efforts to investigate the combined checkpoint inhibition with anti-PD-1/PD-L1 and anti-CTLA-4 have varied to a large number of cancer histologists. Various treatment strategies deliberated for superior clinical efficiency whilst overcoming challenges like treatment resistance and toxicity associated with immunotherapeutic agents [41].

Implementing low-dose combined checkpoint inhibition with nivolumab or ipilimumab in NSCLC appears to be a perspective approach. On the other hand, employing nivolumab prior to ipilimumab in the induction phase for melanoma patients may be an effective strategy to achieve unique results. Findings from various ongoing trials is expected to provide major evidence for validation and facilitate the application of combined checkpoint immunotherapy [42].

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