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LUNG CANCER (H BORGHAEI, SECTION EDITOR)

Combination Immunotherapy in Non-small Cell Lung Cancer

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Abstract

Purpose of Review Checkpoint blockade has changed the treatment landscape in non-small cell lung cancer (NSCLC), but single-agent approaches are effective for only a select subset of patients. Here, we will review the evidence for combination immunotherapies in NSCLC and the clinical data evaluating the efficacy of this approach.

Recent Findings Clinical trials evaluating combination PD-1 and CTLA-4 blockade as well as PD-1 in combination with agents targeting IDO1, B7-H3, VEGF, and EGFR show promising results. Additional studies targeting other immune pathways like TIGIT, LAG-3, and cellular therapies are ongoing.

Summary Combination immunotherapy has the potential to improve outcomes in NSCLC. Data from early clinical trials is promising and reveals that these agents can be administered together safely without a significant increase in toxicity. Further studies are needed to evaluate their long-term safety and efficacy and to determine appropriate patient selection.

Keywords NSCLC · Combination immunotherapy · Checkpoint inhibitors · CTLA-4 · PD-1 · PD-L1

Introduction

The success of single-agent checkpoint blockade has transformed the treatment paradigm of advanced-stage non-small cell lung cancer (NSCLC) in both frontline and platinum refractory settings. We now have three FDA-approved anti-PD-1 and PDL-1 agents for the treatment of metastatic NSCLC after failure of platinum-containing chemotherapy. These agents block a key T cell inhibitory signaling pathway by preventing programmed cell death 1 (PD-1) from binding to programmed cell death ligand 1 or 2 (PD-L1/PD-L2), thereby allowing activation of the previously inactivated T cells [1]. In the second-line setting, all three agents have an overall response rate (ORR) of ~20% with an overall survival (OS) advantage over docetaxel [2••, 3•• 4••, 5••]. Although this ORR is significantly better than seen with previously available second-line chemotherapy options, the real advantage of immunotherapy was seen in the first-line treatment-naïve setting. In a selected population of patients with high PD-L1 expression (PD-L1 ≥ 50%), pembrolizumab was associated with a 44.8% ORR compared to 27.8% of platinum-based chemotherapy [6••]. At the same time, this strategy was not associated with a significant improvement in ORR in an unselected population in the first-line setting (nivolumab was associated with an ORR (26%) and similar progression-free survival (PFS) to platinum-based chemotherapy) [7••, 8•].

Immunotherapy offers many advantages over chemotherapy; improved toxicity profile, better quality of life, and the possibility of a durable long-term response and cure. Despite these advantages, not all patients benefit from immunotherapy. First, only a third of the patients express high PDL-1 (TPS ≥ 50%). Second, the ORR with a single agent remains low and a great majority of patients in the second-line setting (~ 80%) do not respond. Drawing from the experience in melanoma, another immunogenic cancer, many clinical trials in advanced NSCLC are now focusing on immune targets that may be synergistic with checkpoint blockade to improve the overall efficacy and expand the number of patients that may benefit [9, 10].

Immunotherapy has been successfully combined with chemotherapy, leading to FDA approval and widespread use in the first-line setting for metastatic NSCLC without an oncogenic driver mutation [11]. Combination therapies that aim to stimulate the immune system increase the likelihood of an

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immune attack on the tumor by increasing the presence of neoantigens (e.g., radiation therapy) and by helping T cells migrate to the tumor microenvironment (e.g., vaccination). Another strategy to increase the efficacy of immunotherapy is to combine it with other immune modulators including other checkpoints (CTLA-4), and blockade of immune suppressive pathways (LAG-3, TIGIT, etc.). Although there are multiple potential combination modalities that are being explored, this review will focus on strategies that combine different immunotherapy targets.

Combination PD-1/PDL-1 and CTLA-4

The most widely used combination immunotherapy, PD-1/PD-L1 blockade and CTLA-4 inhibitors, had its first success in melanoma. Normally, CTLA-4 expressed on the surface of a T cell binds B7 on an antigen-presenting cell (APC). This interaction blocks B7 from binding CD28, its normal co-stimulatory partner needed for early T cell activation (Fig. 1). Malignant tumor microenvironments have learned to exploit this natural mechanism through overexpression of CTLA-4 to inactivate T cells. PD-1 binding its ligands PD-L1 or PD-L2 also leads to T cell inactivation, but at the later effector phase. Both PD-1 and its ligands are more widely expressed than CTLA-4, leading to effects in immune cells beyond T cells and in different tissue types throughout the body. Targeting multiple phases of T cell activation in many different cell types makes the combination of PD-1 and CTLA-4 blockade appealing [9, 12].

Nivolumab with ipilimumab is the first PD-1/CTLA-4 combination that has demonstrated safety and superior efficacy in metastatic melanoma [9]. Given the early efficacy signals of this combination in metastatic melanoma, clinical trials were initiated for metastatic NSCLC. CheckMate-012 is a phase I trial of nivolumab and ipilimumab as first-line therapy in advanced NSCLC. The initial studies with this combination in NSCLC at the doses used in melanoma showed unacceptable toxicity without significant ORR improvement [13]. Two lower dose regimens were advanced for further clinical study and 78 patients were randomized to nivolumab 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks or every 12 weeks. Although still in early-phase studies, the ORRs, 38 and 47% respectively, compare favorably to single-agent immunotherapy (IO) trials especially given that only 20% of patients had PD-L1 expression of ≥50%. When stratified by PD-L1 status, the ORR was higher in patients with PD-L1 ≥ 1% (57% in both cohorts) and even higher in the PD-L1 ≥ 50% cohort (12 out of 13 patients with a confirmed response) [14•].

Importantly, the rate of grade 3 or 4 treatment-related adverse events (AE) was similar in the two lower dose groups (33 and 37%) as was the rate of treatment discontinuation due to adverse effects (< 10%). Even though this appears low, these rates are higher than those seen in the monotherapy IO trials. The most common reason for discontinuation in both groups was pneumonitis (5%) [15]. These lower dose combination regimens are being evaluated for efficacy in a larger cohort.

Whether or not this strategy will eventually lead to approval in NSCLC remains to be seen. Recently, results from the MYSTIC trial utilizing the same strategy, but different agents, durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA-4), in the first-line setting revealed no improvement for median progression-free survival (mPFS) in patients with PD-L1 ≥ 25% compared to standard of care (SOC) chemotherapy. Overall survival, another primary endpoint, has not yet been reported [16]. NEPTUNE is another clinical trial evaluating the combination of durvalumab with tremelimumab in the first-line setting vs. SOC chemotherapy. No results have been reported from this trial (Table 1) [26].

This strategy has been tested in patients with progression after platinum-based therapy. Ipilimumab in combination with pembrolizumab (Keynote-021, cohort D) was associated with an ORR of 24%. The majority of patients ($n = 45$) received pembrolizumab 2 mg/kg and ipilimumab 1 mg/kg every 3 weeks for four cycles followed by maintenance pembrolizumab. Grade 3 to 4 adverse events were experienced by 24% of patients, most commonly diarrhea. PFS and OS did not change based on PD-L1 status. Overall, the authors concluded that this was similar to the efficacy with single-agent PD-1 therapy, with higher toxicity, and therefore perhaps not a viable option in the relapsed or treatment refractory setting [17].

This strategy is also being specifically evaluated for squamous NSCLC patients in the Lung Master Protocol (Lung-MAP) study (SWOG-1400), which is a multi-arm phase II/III trial looking at novel therapies in the second-line setting. Patients without a targetable mutation can enroll in one of the "non-match" arms looking at combination immunotherapies such as nivolumab plus ipilimumab compared to nivolumab alone. Additionally, combination of tremelimumab and durvalumab is being explored as combination therapy in patients that are refractory to PD-1 therapy. The results have not yet been reported [18].

Combination PD-1/PD-L1 and IDO1

Indoleamine 2,3-dioxygenase 1 (IDO1) is an enzyme that helps to regulate immune function. Increased activity of IDO1 in immune or malignant cells leads to reduced tryptophan in the tumor microenvironment and subsequently decreased cytotoxic T cell activity and increased regulatory T cell activity (Fig. 1). This is hypothesized to be one of the ways that tumors evade the immune system and decrease the T cell response. Inhibitors of IDO1 have been tested in

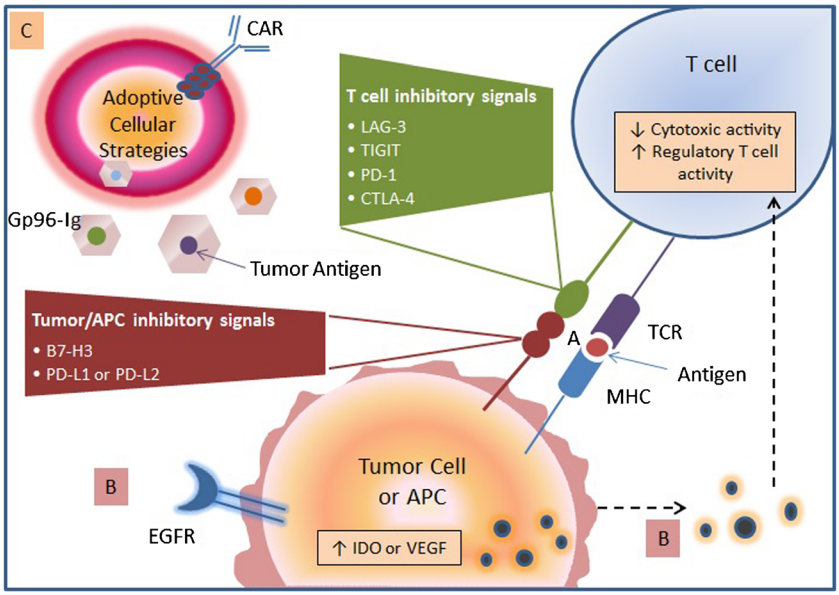

Fig. 1 *Targets and strategies in immunotherapy.* (a) The interaction between a tumor cell or APC (antigen-presenting cell) with a T cell can lead to an activating or inhibiting second signal in the T cell response to an antigen. The inhibitory receptors expressed by the T cell (e.g., LAG-3, TIGIT, PD-1, CTLA-4) or by the tumor/APC (e.g., B7-H3, PD-L1, PD-L2) can tip the balance towards inhibiting a T cell if widely expressed. Many of the novel agents discussed in this article have been designed to block these inhibitory receptors that are often overexpressed in malignancy. (b) Outside of the second signal that determines the response to an antigen, tumor cells can evade the immune system or promote their own growth through increased EGFR (epidermal growth factor receptor) expression and IDO or VEGF production. These are also potential therapeutic targets, especially in combination with checkpoint blockade. (c) Beyond altering a patient's own immune cells in vivo, the infusion of genetically altered T cells (adoptive cellular therapy) through either CAR T (chimeric antigen receptor T cells) or the HS-110 cellular vaccine provides another avenue to alter the immune environment. *Gp96-Ig* heat shock protein chaperoning tumor antigen, *PD-L1/2* programmed cell death ligand 1/2, *IDO* indoleamine 2,3-dioxygenase, *TCR* T cell receptor, *MHC* major histocompatibility complex

combination with standard chemotherapy in breast and pancreatic cancers with mixed results [27, 28]. However, IDO inhibitors may create a more favorable tumor microenvironment for checkpoint blockade and therefore are intriguing partners for PD-1- and CTLA-4-directed therapies.

One of the first IDO1 inhibitors to be tested in combination with checkpoint blockade was GDC-0919 (navoximod), which was combined with the PD-L1 inhibitor, atezolizumab. In a phase I study of 61 patients with advanced solid tumors, the ORR was only 9% [21]. This was reported at ASCO 2017 at the same time that pembrolizumab plus epacadostat, another IDO1 inhibitor, showed a 35% ORR in an IO-naïve NSCLC cohort. PFS data for this cohort is still pending, but has been encouraging for the cohort with metastatic melanoma (ORR 56%, mPFS 12.4 months) [29]. In ECHO-204 combining nivolumab with epacadostat, the ORR and PFS data for NSCLC is pending, but in the squamous cell head and neck cancer cohort presented in May 2017, the disease control rate was reported as 70% in 23 patients. In this cohort, response to therapy was independent of PD-L1 status [20, 30]. Other trials of combination epacadostat with durvalumab, atezolizumab, and chemotherapy are ongoing (Table 1).

As in all combination immunotherapy trials, safety has been a major concern given the unique side effect profile of these agents. The NSCLC cohort of ECHO-202 that received epacadostat 100 mg BID plus pembrolizumab 200 mg every 3 weeks experienced a grade ≥ 3 toxicity rate of 16%, with the most common AE being increased lipase [19]. When epacadostat was combined with nivolumab (ECHO-204), the most common grade ≥ 3 AE was rash (10–12%) [20]. If the early ORR data seen with pembrolizumab plus epacadostat holds true in larger cohorts and remains independent of PD-L1 status, this strategy could be effective in patients who may not have otherwise responded to immunotherapy.

Immunotherapy and B7-H3

B7-H3 (CD276), a membrane glycoprotein, is a member of the B7 family of immune modulatory ligands. It is expressed on antigen-presenting cells, and even though it was thought to be immune co-stimulatory, more recent evidence reveals a role in inhibition of T cells and immune evasion (Fig. 1) [31–33]. Additionally, B7-H3 plays a role in cancer progression including invasion and migration, angiogenesis, and gene regulation via epigenetic modifiers. The prevalence of B7-H3 overexpression across lung, breast, brain, kidney, and prostate cancers has been linked with a worse prognosis. The selective expression of B7-H3 on tumor cells makes it an attractive target. MGA271 (enoblituzumab) is a humanized IgG1 monoclonal antibody-targeting B7-H3 (CD276), a member of the B7 family. Phase I

Table 1 Summary of combination immunotherapy trials in NSCLC

Trial	Drugs	Phase	Histology	Line of therapy	ORR	mPFS (months)	mOS (months)	Grade ≥ 3 AE	Notes
PD-L1+ CTLA-4									
CheckMate-012	Nivo 3 mg/kg q 2 wk Ipi 1 mg/kg q 12 wk	I	NSCLC	1st-line	47%	8.1	NR	37%	PD-L1 ≥ 1% had ORR 57% [14, 15]
	Nivo3mg/kg q 2 wk Ipi 1 mg/kg q 6 wk	I	NSCLC	1st-line	38%	3.9	NR	33%	
Keynote-021D	Pembro + Ipi	I/II	NSCLC	≥ 2nd-line	24%	6	17	24%	[17]
MYSTIC	Durva + Treme vs. Durva vs. SOC	III	NSCLC	1st-line	P	P[1]	P	P	
NEPTUNE	Durva + Treme vs. SOC	III	NSCLC	1st-line	P	P	P	P	
Lung-MAP (SWOG1400)	Nivo ± Ipi Durva + Treme	II/III II	NSCLC (sq)	≥ 2nd-line	P	P	P	P	[18]
PD-1/PD-L1 + IDO1									
ECHO-202	Pembro + epacadostat	I/II	NSCLC	≥ 2nd-line	35%	P	P	16%	[19]
ECHO-204	Nivo + epacadostat	I/II	Advanced cancers (includes NSCLC)	≥ 2nd-line	P	P	P	10–12%[1]	[20]
GDC-0919	Atezo + GDC-0919	I		≥ 2nd-line	9%			13%	[21]
PD-1/PD-L1 + VEGF									
	Pembro + ramucirumab	I	NSCLC	≥ 2nd-line	30%	P	P	7%	*n* = 27 DCR 80% [22]
	Pembro + lenvatinib	I	Advanced solid tumors (includes NSCLC)	≥ 2nd-line	See note			MTD found[2]	1/2 NSCLC patients responded [23]
PD-1/PD-L1 + EGFR									
PD-1 + EGFR	Pembro + necitumumab	Ib	NSCLC	≥ 2nd-line	23.4%	4.1	6-month OS: 78.8%	20% with tx AEs	[24, 25]

NSCLC non-small cell lung cancer, *ORR* overall response rate, *mPFS* median progression-free survival, *mOS* median overall survival, *NR* not reached, *Nivo* nivolumab, *Ipi* ipilimumab, *Pembro* pembrolizumab, *Durva* durvalumab, *Treme* tremelimumab, *Atezo* atezolizumab, *P* pending results, *sq* squamous, *SOC* standard of care chemotherapy, *tx* therapy, *AE* treatment-related adverse event, *q* every, *wk* weeks, *DCR* disease control rate

[1] For rash, the most common treatment-related adverse event

[2] Maximum tolerated dose = pembrolizumab 200 mg q 3 wk + lenvatinib 20 mg/day

clinical trial results of single-agent MGA271 in multiple tumor types report tolerability and tumor shrinkage (2–69% at 12 weeks) across several tumor types [34].

A monoclonal antibody against B7-H3 labeled with iodine-131 for intratumoral delivery of radiation has shown promise in preclinical studies and is being investigated in phase I trials. MGD009, a dual-affinity re-targeting protein bispecific for B7-H3 and CD3, is also being investigated [35]. Based on promising single-agent activity, and a role in the immune pathway, combination therapies with other checkpoint inhibitors, such as pembrolizumab (NCT 02475213) and ipilimumab (NCT02381314), are being evaluated.

Immunotherapy, TIGIT, and LAG-3

Lymphocyte activation gene 3 (LAG-3) is an immune inhibitory receptor expressed on activated T cells. Recent studies have revealed that LAG-3 and PD-1 are co-expressed on tumor-infiltrating lymphocytes, suggesting that they may contribute to tumor-mediated immune suppression (Fig. 1) [36]. Regulatory T cells (Tregs) expressing LAG-3 have enhanced suppressive activity, whereas cytotoxic CD8+ T cells expressing LAG-3 have reduced proliferation rates and effector cytokine production. LAG-3 blockade has been associated with restoration of T cell cytotoxic activity, an effect that is synergistic with PD-1 blockade [37]. Multiple clinical trials of antagonistic LAG-3 agents in combination with anti-PD-1 and/or anti-CTLA-4 therapy are ongoing.

Like LAG-3, TIGIT (T cell immunoreceptor with Ig and ITIM domains) is an inhibitory immune receptor expressed on lymphocytes that is studied in the context of immune evasion in cancer. It has been hypothesized that TIGIT can inhibit immune cells at multiple steps in the cancer immunity cycle, by preventing initial tumor cell death and release of cancer cell antigens, suppression of dendritic cell, and co-stimulatory abilities, and TIGIT+ T cells can suppress CD8+ T cell effector function [38]. Inhibition of TIGIT can therefore enhance antitumor T cell responses. TIGIT inhibitors are still in early-phase development, but at least two agents (MTIG7192A, OM*P*-313M32) are being investigated in phase I trials.

Cellular Therapies: Heat Vaccine Trial and CAR T Cell Therapy

Viagenpumatucel-L (HS-110) is an allogeneic cell-based therapeutic cancer vaccine composed of a cell line expressing a repertoire of tumor antigens (MAGE-A3, NY-ESO-1, LAGE-1, and others) that are chaperoned by a modified, secretable, heat shock protein (gp96-Ig), leading to CD8+ T cell activation in response to antigen delivery (Fig. 1). Combination of such an approach with anti-PD-1 therapy may be synergistic, by increasing antigen presentation and possibly efficacy of T cells (NCT02439450). Another approach using a personalized tumor neo-antigen-specific vaccine with pembrolizumab is being evaluated in NSCLC. The vaccine is given in conjunction with poly-ICLC, a synthetic complex of carboxymethylcellulose, polyinosinic-polycytidylic acid, and poly-L-lysine double-stranded RNA that stimulates production of interferon-gamma (NCT03166254).

Chimeric antigen T cell receptor (CAR T cell) therapy, another form of adoptive cell therapy (ACT), has seen recent success in hematologic malignancies. In NSCLC, this is potentially another way to directly alter the immune environment through infusion of a patient's own genetically altered T cells directed at antigens expressed on malignant cells. There are trials underway in lung cancer with CAR T cell therapy targeting mesothelin, PD-L1, ROR1, MUC1, CEA, EGFR, FAP, GD2, GPC3, and HER2 [39]. In their more established role in hematologic malignancies, the addition of checkpoint blockade to failing CAR T cells shows promise in reinvigorating a response [40]. Therefore, if successful in NSCLC, CAR T cells may work synergistically with other agents targeting the immune system.

Immunotherapy and VEGF

Vascular endothelial growth factor (VEGF) has a well-established role in angiogenesis and is increasingly being recognized as a modulator of the immune response. Increased VEGF produced by malignant cells can directly expand the Treg population, stall the maturation of tumor antigen-presenting dendritic cells, and affect lymphocyte trafficking across the endothelium as well as indirectly inhibit the tumor-directed T cell response through expansion of myeloid-derived suppressor cells, which act through a variety of mechanisms including increased IDO production [41–44]. In preclinical mouse models of melanoma, the addition of anti-VEGF therapy to adoptive T cell transfer or a GM-CSF secreting tumor cell vaccine led to increased T cell recruitment and prolonged survival [45, 46].

The first clinical trial utilizing this strategy in metastatic melanoma combined ipilimumab with bevacizumab (anti-VEGF). The combination was safe and tumor biopsies revealed activated vessel endothelium along with increased CD8+ T cells and macrophage recruitment. The disease control rate was 67.4% in this mostly pre-treated population [47]. A variety of clinical trials investigating anti-VEGF therapy with checkpoint blockade are ongoing in NSCLC. Bevacizumab plus chemotherapy is being investigated with atezolizumab (NCT02366143) or pembrolizumab (NCT02039674) in the first-line setting. After induction chemotherapy, the role of nivolumab as maintenance therapy with or without bevacizumab is being evaluated in the multi-arm CheckMate 370 and 012 trials (NCT02574078, NCT01454102—arm D).

A phase I study with another anti-VEGF monoclonal antibody, ramucirumab, plus pembrolizumab in advanced solid tumors is underway. Interim results show a 30% ORR across multiple tumor types and a 7% rate of grade 3 to 4 AEs [22]. Lenvatinib, an oral small molecule inhibitor of VEGF, in combination with pembrolizumab is still in the dose finding phase, but initial phase I results show promising ORRs (~ 50%) across multiple advanced solid tumors (Table 1) [23]. Overall, the addition of VEGF to checkpoint blockade in NSCLC appears safe, but the efficacy of this combination will need further validation in larger cohorts.

Immunotherapy With Targeted Therapy

There is mounting evidence that therapies targeting oncogenic driver mutations can also alter the tumor microenvironment. Patients with BRAF-mutated metastatic melanoma treated with BRAF or BRAF/MEK inhibitors were found to have increased CD8+ T cell infiltration and up-regulation of PD-1/PD-L1 after treatment, suggesting potential synergy between targeted and immunotherapy approaches [48]. This observation in BRAF V600E-mutant melanoma can be applied to other solid tumors including NSCLC with and without driver mutations.

The EGFR-directed tyrosine kinase inhibitors osimertinib, erlotinib, and gefinitib have been tested in combination with checkpoint blockade in the EGFR-mutant population. The TATTON trial is investigating osimertinib combinations. Although osimertinib was safely combined with savolitinib (MET inhibitor) and selumetinib (MEK 1/2 inhibitor), the increased rate of interstitial lung disease (38%) in the durvalumab plus osimertinib arm led to early suspension of that arm of the study [24]. Other EGFR and PD-1/PD-L1 combinations have also seen increased toxicity. Erlotinib in combination with nivolumab had a grade 3–4 toxicity rate of 24% and geftinib plus durvalumab had an increase in grade 3–4 transaminitis (40–70%) [25, 49].

Given the potential immune modulating effects of EGFR inhibition in combination with checkpoint blockade, this approach has also been investigated in EGFR wild-type patients as well. In the phase I study of pembrolizumab (anti-PD-1) and necitumumab (anti-EGFR antibody), 61 pre-treated NSCLC patients were treated with the combination. As of September 2017, the ORR was 23.4% and mPFS was 4.1 months (Table 1). Half of the patients in the study had negative PD-L1 staining, which also corresponded to a lower ORR (4 patients, 12.5%). Patients with weakly to strongly positive PD-L1 had a higher ORR (25 and 40%, respectively). This was based on only seven patients that responded in these groups so the effect of PD-L1 on outcome remains to be determined [50].

The most common grade ≥ 3 AEs were rash (9%), hypomagnesemia (9%), venous thromboembolism (9%), and increased lipase (9%). The rate of treatment discontinuation due to AEs was 14.7% and one patient died because of an acute respiratory infection that was attributed to treatment [51]. There is not enough evidence at this point to support the use of targeted therapies with an IO agent. Toxicity remains an issue and clinical efficacy is not clearly better. This approach remains investigational.

Patient Selection

One of the major challenges for immunotherapy in NSCLC is appropriate selection of patients that have the highest likelihood of benefit. PD-L1 staining is the only clinically available and validated predictive biomarker, but its utility is limited. Durable responses have been seen in patients without PD-L1 expression and standardized interpretation of the test across assays and operators has been challenging. Tumor mutational burden (TMB) has emerged as an independent predictor of response to immunotherapy and may play a larger role in patient selection in the near future [52]. The Blood First Line Ready Screening Trial (B-F1RST) is an ongoing clinical trial looking at the predictive value of TMB detected in the blood in patients treated with first-line atezolizumab. The primary endpoint is ORR as well as determining if there is a relationship between efficacy (PFS) and TMB levels [53]. Gene expression profiling (GEP) is another potential biomarker. An upcoming clinical trial, KeyIMPACT (KN-495) will randomize patients with newly diagnosed metastatic NSCLC to combination immunotherapies based on GEP and TMB.

Other markers such as the presence of CD8+ T cells in the tumor microenvironment and the degree of IFN-γ signaling (IFN-γ signature) are currently not clinically available, but may eventually play a role in patient care [54]. This will be especially important in evaluating the success of combination IO since many of the additional targets aim to draw more T cells into the tumor microenvironment.

Safety

Combination immunotherapy has brought with it some unique safety concerns. Although the vast majority of IO side effects can be mitigated with steroids and a treatment break, some side effects require permanent discontinuation of treatment or can be life-threatening. Overall, combination PD-1/PD-L1 and CTLA-4 inhibition does have a higher rate of grades 3 to 4 AEs. Initially, the rate of AEs in NSCLC patients led to dose reductions compared to the melanoma dosing. Even at the lower doses used in the expansion cohort, the rate of grade ≥ 3 AEs was around 30%.

The most concerning side effect of immunotherapy in lung cancer is immune-related pneumonitis given that many patients with lung cancer start out with compromised lung function from smoking, presence of emphysema, or disease burden. Despite a high overall AE rate, there were no cases of grade 4 pneumonitis reported in patients treated with combination ipilimumab and nivolumab [14•]. The phase I study of this combination reported a similar rate of grades 3 to 4 pneumonitis compared to nivolumab alone (3–5 vs. 3%). Even with this low rate, pneumonitis was the most common reason for discontinuation of the combination at any grade. Diarrhea was also increased in patients treated with the combination vs. nivolumab alone (21 vs. 8%) and the incidence of colitis was similarly elevated (3–5 vs. 1%). However, the increased incidence of colitis and pneumonitis with combination therapy can be partially mitigated with the appropriate dosing schedule. Patients treated with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 12 weeks had a similar side effect profile to nivolumab alone with superior efficacy (ORR 47 vs. 26%). This highlights the need for flexible dose finding trial designs in early-phase trials of these combination immunotherapies.

Conclusions

Combining novel immune targets with checkpoint blockade has the potential to bring the benefits of immunotherapy to more patients. Although the response rates for many of these combinations are encouraging, validation in larger studies is needed. With better response rates comes increased toxicity as well as greater risk for devastating treatment-related adverse events. Predicting which patients may benefit from combination immunotherapy and avoid serious adverse events remains elusive.

As more of these combinations get closer to FDA approval, it will take time for them to find their appropriate place in the treatment of NSCLC. The sequence of treatment has not been well studied and limited data exists for the risks and benefits over single-agent IO. In addition, combination immunotherapy and cellular therapies will likely be very costly to the health system. Combining immune-directed modalities may become cost prohibitive with marginal overall survival benefit.

Despite the lack of long-term and robust efficacy data, potentially high cost, and an uncertain place in the treatment paradigm, a multi-pronged approach to resetting the immune system to fight cancer remains compelling. Although immunotherapy will not be able to help every patient, these innovative strategies hold promise for many NSCLC patients.

Compliance with Ethical Standards

Conflict of Interest Melina E. Marmarelis and Charu Aggarwal declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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