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New Drugs

Immunotherapy-based combinations in metastatic NSCLC

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ABSTRACT

Immuno-oncology has revolutionized the treatment of metastatic non-small cell lung cancer (mNSCLC) since the approval of immunotherapy by the U.S. FDA in 2015. Despite the advancements, outcomes for patients have room for further improvement. Combination therapies have shown promise in overcoming resistance and improving outcomes. This review focuses on current immunotherapy-based combination approaches, reported and ongoing trials, as well as novel combination strategies, challenges, and future directions for mNSCLC treatment. We summarize approaches in combination with chemotherapy, novel immune checkpoints, tyrosine kinase inhibitors and other strategies including vaccines, and radiation therapy. The promise of biomarker-driven studies to understand resistance and design multi-arm platform trials that evaluate novel therapies is becoming of increasing relevance with the ultimate goal of administering precision immunotherapy by identifying the right dose of the right combination for the right patient at the right time.

Introduction

Since the first approval of immunotherapy in 2015 by the U.S. FDA, the advent of immunotherapy has changed the treatment paradigm of metastatic non-small cell lung cancer (mNSCLC) [1]. With increased lung cancer screening efforts, and approvals for use of anti-Programmed Death-1 (PD-1)/ Programmed Death-Ligand 1 (PD-L1) antibodies in the unresectable locally advanced disease and the perioperative setting, the use of immunotherapy will continue to increase in the coming decade [2,3].

Despite advances with immunotherapy, the outcomes for patients with mNSCLC have room for improvement with 5-year survival of 30% with the use of single agent immunotherapy in biomarker-selected (high PD-L1 expression) [4] and 10–20% in biomarker-unselected patients receiving immunotherapy frontline or later.[5] Additionally, as most patients develop primary or acquired resistance to current immunotherapies, discovery of novel immunotherapy targets and modalities represent both an unmet need and an opportunity to improve outcomes. Thus, rational combinations of immunotherapy to improve clinical outcomes for patients with mNSCLC are a priority.[6].

In this review, we will focus on various immunotherapy-based combination approaches which are currently approved for clinical use and discuss reported and ongoing trials (Table 1). We will also discuss novel immunotherapy combination approaches (Fig. 1), challenges, and future directions for immunotherapy-based combinations in mNSCLC.

Chemoimmunotherapy combinations

Although the initial clinical development of immunotherapy focused on anti- PD-1 receptor and anti-programmed death ligand-1 PD-L1 monotherapy in the second line[5], there has been recent progress in harnessing immunotherapy in combination with chemotherapy in the first-line setting. Chemotherapy might theoretically have a synergistic effect by increasing the neo antigen load for recognition by T-cells, with immunotherapy inhibiting the T-cell checkpoints to enhance antitumor immunity.[7,8].

Currently, there are several approvals for chemoimmunotherapy both in squamous and nonsquamous histology, and in PD-1/PD-L1 high and low tumor types. Pembrolizumab in combination with platinum-based chemotherapy is approved both in squamous and nonsquamous histology based on KEYNOTE-407[9] and KEYNOTE-189[10] showing overall survival benefits. Similarly, studies with atezolizumab and cemiplimab in combination with chemotherapy have led to regulatory approvals in the frontline therapy for non-oncogene drive advanced NSCLC.[11,12].

With other agents showing similar benefit, and potential pending large or regional regulatory approvals (namely tislelizumab[13], toripalimab [14], camrelizumab[15], and sintilimab[16,17]), there is a

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Table 1

NCT Identifier (Trial Name)	Phase	Investigational Agent	Mechanism of Action of Investigational Agent	Setting	Current Status
Dual Checkpoint inhibitor combinations					
LAG3 based combinations					
NCT04618393	I/II	EMB-02	Anti-PD-1/LAG-3 bispecific mAb	Pretreated	Recruiting
NCT04140500	I	RO72747669	Anti-PD-1/LAG-3 bispecific mAb	Pretreated	Recruiting
NCT03849469	I	XmAb22841+- Pembrolizumab	Anti-CTLA-4/LAG-3 bispecific mAb	Pretreated	Active, not recruiting
NCT03250832	I	TSR-033 +- Dostarlimab	Anti-LAG3 mAb	Pretreated	Active, not recruiting
TIGIT based combinations					
NCT04672369	I	IBI939	Anti-TIGIT mAb	Pretreated	Recruiting
NCT04995523	II	AZD2936	Anti-PD-1/TIGIT bispecific mAb	Pretreated	Recruiting
NCT05102214	I/II	HLX301	Anti-PD-1/TIGIT bispecific mAb	Pretreated	Recruiting
NCT04761198	I/II	Etigilimab + Nivolumab	Anti-TIGIT mAb	Pretreated	Recruiting
NCT04738487 (KEYVIBE-003)	III	MK-7684A (Vibostolimab)/Pembrolizumab vs. Pembrolizumab	Anti-TIGIT mAb	First-Line	Recruiting
NCT04746924	III	Ociperliamab/Tislelizumab vs. Pembrolizumab	Anti-TIGIT mAb	First-Line	Recruiting
NCT04736173 (ARC-10)	III	Zimberelimab + Domvanalimab vs. Zimberelimab vs. Chemotherapy	Anti-TIGIT mAb	First-Line	Recruiting
NCT05502237 (STAR-121)	III	Zimberelimab + Domvanalimab + Chemotherapy vs. Pembrolizumab + Chemotherapy	Anti-TIGIT mAb	First-Line	Recruiting
TIM3 based combinations					
NCT02817633	I	TSR-022 + nivolumab or TSR-042 or TSR-033	Anti-TIM3 mAb	Pretreated	Recruiting
NCT03708328	I	RO7121661	Anti-PD-1/TIM-3 bispecific mAb	Pretreated	Active, not recruiting
GITR based combinations					
NCT03126110	I/II	INCAGN01876 + Anti-PD-1 mAb/Anti-PD-1 + Anti-CTLA-4 mAb	GITR agonist mAb	Pretreated	Completed
NKG2A based combinations					
NCT05221840	III	Durvalumab + Monalizumab vs. Durvalumab + Placebo	Anti-NKG2A mAb	Stage III unresectable	Recruiting
Immunotherapy and Tyrosine Kinase inhibition					
NCT02607813	I	Spartalizumab plus LXH254	Pan-RAF inhibitor	Pretreated	Completed
NCT03689855	II	Atezolizumab plus ramucirumab	Anti-VEGF mAb	Prior ICI	Active, not recruiting
NCT03527108	II	Nivolumab plus ramucirumab	Anti-VEGF mAb	Prior ICI	Recruiting
NCT03472560	II	Avelumab plus axitinib	Anti-VEGF TKI	Prior ICI	Active, not recruiting
NCT04046614	I/II	Nivolumab plus nintedanib	Anti-VEGF TKI	Prior ICI	Active, not recruiting
NCT03581487	I/II	Durvalumab plus tremelimumab plus selumetinib	Anti-MEK TKI	Pretreated	Recruiting
NCT03225664	I/II	Pembrolizumab plus trametinib	Anti-MEK TKI	Pretreated	Active, not recruiting
NCT03991819	I	Pembrolizumab plus binimetinib	Anti-MEK TKI	First-Line	Recruiting
NCT03829319 (LEAP-006)	III	Platinum-pemetrexed plus pembrolizumab plus lenvatinib or placebo	Anti-VEGF TKI	First-Line	Active, not recruiting
NCT03976375 (LEAP-008)	III	Pembrolizumab plus lenvatinib vs. docetaxel	Anti-VEGF TKI	Post-CT and ICI	Active, not recruiting
NCT03906071 (SAPPHIRE)	III	Nivolumab plus sitravatinib vs. docetaxel	Anti-VEGF TKI	Post-CT and ICI	Active, not recruiting
Novel Immunotherapy Combinations					
Vaccine based combinations					
NCT03289962	I	Autogene Cevumeran + atezolizumab	Neoantigen-specific vaccine	Pretreated and First-Line	Active, not recruiting
NCT02439450	I/II	Viagenpumatucel-L + nivolumab	Neoantigen-specific vaccine	Pretreated	Completed
NCT02823990	II	TG4010 + nivolumab	Neoantigen-specific vaccine	Pretreated	Completed
Cytokine based combinations					
NCT03228667	II	N-803 + ICI	IL-15 superagonist	Pretreated	Active, not recruiting
NCT03207867	II	NIR178 + Spartalizumab	A2AR antagonist	Pretreated	Active, not recruiting
NCT02740985	I	AZD4635 + durvalumab	A2AR antagonist	Pretreated	Active, not recruiting
NCT05221840	III	Durvalumab + Oleclumab vs. Durvalumab + Placebo	Anti-CD73 mAb	Stage III unresectable	Recruiting
DNA damage repair inhibitor based combinations					
NCT03775486 (ORION)	II	Durvalumab + SOC followed by Durvalumab/Olaparib maintenance vs Durvalumab + SOC followed by Durvalumab/placebo maintenance	PARP inhibitor	First line	Active, not recruiting
NCT03976323 (KEYLINK 006)	III	Pembrolizumab + SOC followed by Pembrolizumab /Olaparib maintenance vs Pembrolizumab + SOC followed by Pembrolizumab /placebo maintenance	PARP inhibitor	First line	Active, not recruiting

(*continued on next page*)

growing armamentarium of anti-PD-1/PD-L1 agents. The next frontier of challenges for anti-PD-1/PD-L1 based chemoimmunotherapy combinations include tackling the issue of regulatory approvals based on population included in clinical trial conduct, access and global availability, and financial toxicity with cost related to treatment.[18,19].

DUAL immunotherapy combinations

Anti PD-1/PD-L1 and Anti-CTLA4

Since the discovery of cytotoxic lymphocyte antigen-4 (CTLA-4) as a critical switch controlling T-cell responses, CTLA-4 blockade has been utilized to increase antitumor immunity.[20] In 2015, the first combination of anti-CTLA-4 (ipilimumab) and anti-PD-1 antibody (nivolumab) was FDA-approved for patients with metastatic melanoma.[21] Subsequently, there has been increasing interest to test this immunotherapy combination for patients with advanced NSCLC, with 2 and 3 of these different combinations currently EMA and FDA approved respectively.

CHECKMATE-227 studied benefit of nivolumab plus ipilimumab compared to chemotherapy in patients' stage IV with no known EGFR or ALK alterations NSCLC who had no prior systemic therapy. Patients were stratified based on histology, with primary independent endpoints being PFS in high tumor mutation burden (TMB) population and OS in PD-L1 $\geq$ 1%.[22] The 5-year update analysis shows OS benefit with nivolumab plus ipilimumab compared to chemotherapy in both PD-L1 + (17.1 months vs. 14.9 months) and PD-L1 – (17.4 months vs 12.2 months).[23].

Nivolumab in combination with ipilimumab and platinum-doublet chemotherapy was evaluated in the CHECKMATE-9LA trial, in which 719 patients were randomly assigned to either two cycles of platinum-doublet chemotherapy plus nivolumab and ipilimumab (until progression), or four cycles of platinum doublet chemotherapy without immunotherapy. [24] Patients receiving nivolumab/ipilimumab/chemotherapy experienced improved median OS (15.6 vs. 10.9 months), which remained consistent at 3 years of follow-up (15.8 vs. 11.0 months).[25].

Most recently, POSEIDON trial reported another combination of anti CTLA-4 antibody tremelimumab with anti PD-L1 antibody durvalumab, along with platinum-based chemotherapy.[26] Tremelimumab/durvalumab/chemotherapy demonstrated a statistically significant and clinically meaningful improvement in OS compared to chemotherapy alone (14 vs.11.7 months), which led to its FDA approval.

In all three trials, a specific similar activity of the combinatorial therapy was observed in negative PD-L1 NSCLC patients as compared to PD-L1 positive ones, which was not observe using treatments based on the backbone of anti PD(L)-1 agents in absence of the CTLA-4 component. Furthermore, these combination strategies have been shown to be well-tolerated in large population with metastatic NSCLC and in patients age 75 years or older.[27].

Despite these encouraging results, some specific studies such as MYSTIC (durvalumab with or without tremelimumab compared to standard chemotherapy) [28], NEPTUNE (durvalumab with tremelimumab compared to standard chemotherapy)[29] and KEYNOTE-598 (pembrolizumab with ipilimumab compared to pembrolizumab with placebo) did not able to demonstrate significant improvement in outcomes in the subpopulations specifically defined for their primary endpoints.[30].

Anti-PD-1/PD-L1 and Anti-LAG3

LAG3 (Lymphocyte-activation gene 3), also known as the 3rd checkpoint, is expressed. It is expressed on the surface of effector T cells and regulatory T cells (Tregs) and plays a crucial part in the adaptive immune response, limiting T-cell function, TCR signaling and maintaining homeostasis.[31] Anti-LAG3/Anti-PD-1 combination has shown to have synergistic activity in tumor models.[32] Based on this rationale, Relatlimab (a LAG-3 blocking antibody) was combined with nivolumab in RELATIVITY-047, a trial comparing relatlimab and nivolumab combination with nivolumab alone for patients with previously untreated metastatic or unresectable melanoma. relatlimab/nivolumab combination improved PFS (10.1 vs. 4.6 months) subsequently leading to the first FDA approval for an anti-LAG3 molecule in solid tumors.[33].

For NSCLC, the combination of relatlimab and nivolumab is currently being studied in RELATIVITY-104, a phase 2, randomized, double-blind study comparing this combination with chemotherapy to nivolumab plus chemotherapy in stage IV recurrent NSCLC (NCT04623775).[34] Another LAG-3 inhibitor, ieramilimab was tested in a phase 1 study for the treatment of patients with advanced/metastatic solid tumors with or without the anti-PD-1 antibody, spartalizumab.[35] Antitumor activity was observed in the combination arm, with 3 (2%) complete responses and 10 (8%) partial responses across the cohort. Although, ieramilimab was well tolerated as monotherapy and in combination with spartalizumab, the antitumor activity was modest. Within the NSCLC cohort, the ORR was 15% and 0% for patients with anti-PD-1/-L1 naïve and refractory NSCLC respectively.

Another mechanism to harness the LAG3 axis, is to activate the antigen presenting cells that express MHC class II via its corresponding ligand LAG3.[36] The MHC class II agonist eftilagimod alpha (efti, IMP321 or LAG-3Ig) is a soluble LAG-3 protein that activates APC leading to CD8 T-cell activation.[36] The addition of an anti PD-1 immune checkpoint inhibitor can then further enhance activity by combining efti's activating effects on immune cells with the release of immune inhibitory effects. TACTI-mel phase 1 trial demonstrated good safety and efficacy for patients with anti PD-1 naïve and refractory metastatic melanoma.[37] TACTI-002 is a phase 2 study investigating eftilagimod alpha (efti) in first-line metastatic NSCLC in combination with pembrolizumab. Efti was given at dose of 30 mg subcutaneously every 2 weeks for 8 cycles and then every 3 weeks for 9 cycles, while pembrolizumab was given every 3 weeks in combination and as maintenance therapy for 16 cycles. The ORR for the cohort (n = 114) was 37.7%, with patients having PD-L1 $\geq$ 50% having the most benefit (52.6%).[38].

Anti-PD-1/PD-L1 and Anti-TIGIT

T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) is an immune checkpoint and inhibitory receptor which

Table 1 (*continued*)

NCT Identifier (Trial Name)	Phase	Investigational Agent	Mechanism of Action of Investigational Agent	Setting	Current Status
NCT04475939 (ZEAL-1L)	III	Pembrolizumab /Niraparib maintenance vs Pembrolizumab /placebo maintenance	PARP inhibitor	First line	Recruiting
NCT03330405	I	Avelumab + Talazoparib	PARP inhibitor	Pretreated	Active, not recruiting
NCT03334617 (HUDSON)	II	Durvalumab + Ceralasertib	ATR inhibitor	Pretreated	Recruiting
NCT04216316	IB/II	Pembrolizumab + Chemotherapy + Berzosertib vs. Pembrolizumab + Chemotherapy	ATR inhibitor	First-Line	Recruiting

negatively regulates CD226 signaling pathway, essential for NK and CD8 + T cells activation.[39] It is expressed on multiple immune cells including CD4, CD8, T stem-like memory cells and NK cells. It is enriched in tumor tissues and has been shown to have prognostic impact across different type of cancers.[40] It is hypothesized that combining TIGIT blockade with PD-1/PD-L1 may redirect differentiation of activated T cells to effector/memory T cells.

CD226 expression has been associated with clinical benefit in patients with NSCLC treated with anti-PD-L1 antibody atezolizumab.[41] Mechanistically, PD-1 inhibits phosphorylation of both CD226 and CD28 via its ITIM-containing intracellular domain (ICD); with TIGIT restricting CD226 co-stimulation by blocking interaction with their common ligand PVR (CD155). Thus, full restoration of CD226 signaling, and optimal anti-tumor CD8 + T cell activity requires blockade of TIGIT and PD-1, providing a mechanistic rationale for combinatorial targeting in the clinic.[42].

The initial results of activity of combination therapy with novel anti-TIGIT molecule, tiragolumab and atezolizumab was assessed in the CITYSCAPE trial, a phase 2 placebo controlled trial in patients with chemotherapy naive, PDL1 positive mNSCLC.[43] Patients were randomly assigned to receive tiragolumab plus atezolizumab versus placebo plus atezolizumab every 3 weeks with study co-primary endpoints being ORR and PFS. The combination demonstrated clinically meaningful improvement in ORR (31.3% vs. 16.2%, p = 0.031) and median PFS (5.4 vs. 3.6 months, p = 0.015) compared to placebo in patients with chemotherapy-naive, PD-L1-positive mNSCLC. Notably, the PFS benefit was driven by the subgroup of PD-L1 TPS > 50%, with an absence of ORR and PFS benefit observed in those patients with PD-L1 TPS 1–49% - with 12 month PFS rates of 51% vs 25% respectively.[43] Based on these encouraging results, the FDA granted a breakthrough therapy designation to tiragolumab. A confirmatory phase 3 study SKYSCRAPER-01 is currently underway evaluating tiragolumab plus atezolizumab versus atezolizumab alone in first-line PD-L1-high mNSCLC. Although press release reports revealed that this study did not meet its co-primary endpoint of PFS, OS data are eagerly awaited.

Another anti-TIGIT molecule in development, vibostolimab (MK7684) is a humanized immunoglobulin G1 monoclonal antibody targeting TIGIT. This was evaluated in the KEYVIBE-001 phase 1 study of vibostolimab monotherapy or in combination with pembrolizumab.[44] In part A (dose escalation), no dose-limiting toxicities were observed in either the monotherapy or combination group. In part B (dose expansion), 106 patients with NSCLC were enrolled with anti–PD-1/PD-L1-naïve patients receiving combination therapy and anti–PD-1/PD-L1-refractory patients receiving either monotherapy or combination therapy. The ORR was higher for PD-L1 TPS > 1% (33%) compared to those < 1% (27%) with an overall ORR of 26% in patients who had not received prior anti-PD-1/PD-L1. Among the anti-PD-1/PD-L1 refractory patients, the responses were suboptimal in both the monotherapy (3%) and combination arms (3%).

Most recently, the ARC-7 trial evaluated the addition domvanalimab, an anti-TIGIT monoclonal antibody, with the anti–PD-1 monoclonal antibody zimberelimab with or without the adenosine receptor antagonist etrumadenant in patients with PD-L1–high mNSCLC. This study demonstrated domvanalimab (AB154) plus zimberelimab (AB122) with or without etrumadenant (AB928) generated an improvement in ORR (40% vs 27%) and PFS (10.9 vs 5.4 months, HR = 0.65, 95% CI, 0.37–1.1) compared with zimberelimab alone in patients with PD-L1–high mNSCLC. Immune-related TEAEs occurred in 48%, 47%, and 60% of patients in the zimberelimab monotherapy, doublet, and triplet arms, respectively.[45] The combination of domvanalimab and

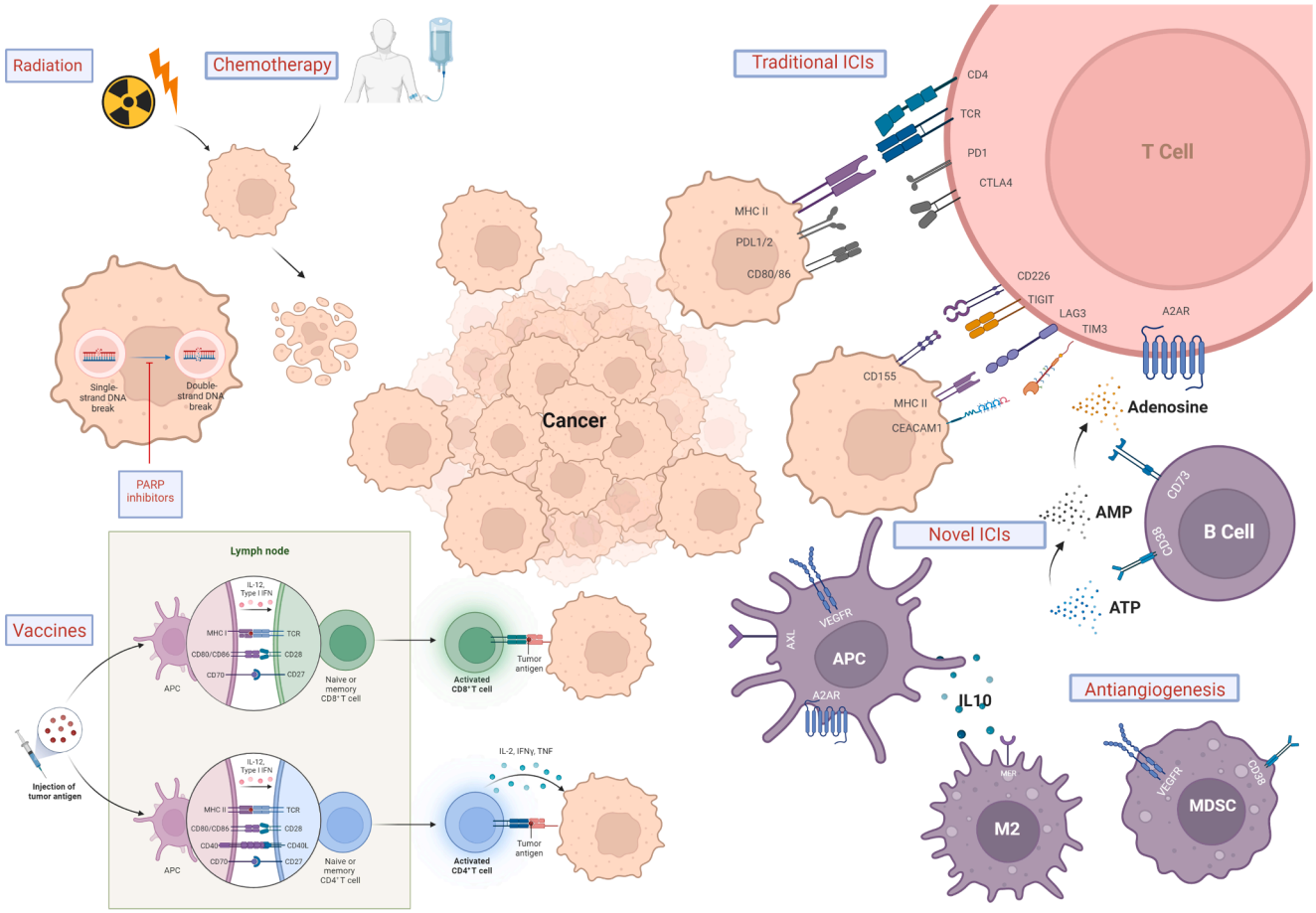

Fig. 1. Immunotherapy based combination approaches in metastatic NSCLC.

zimberelimab is under further investigation in patients with NSCLC in the phase 3 ACR-10 (NCT04736173) and STAR-121 (NCT05502237) trials. Domvanalimab will also be evaluated in combination with durvalumab following concurrent chemoradiation for patients with stage III unresectable NSCLC in the ongoing PACIFIC-8 study (NCT05211895).

Anti-PD-1/PD-L1 and Anti-TIM3

T cell immunoglobulin and mucin domain-containing protein 3 (TIM3), first discovered in 2002 is a member of the TIM family of immunoregulatory proteins. Tim-3 is a receptor that is expressed on IFN-γ-producing T cells, FoxP3 + Treg cells, macrophages and dendritic cells where it has been shown to suppress their responses upon interaction with their ligands. TIM3 blockade may improve responses[46] while also being synergistic with anti-PD-1 blockade.[47] $TIM3^{+}$ T_{reg} is an abundant T_{reg} population, which when present correlates with tumor severity and progression.[48] Since TIM3 expression is limited to terminally differentiated T-cells and restricted to intratumoral T_{reg}, it has less cytotoxicity than other checkpoints such as CTLA-4.[49]However, TIM3 blocking antibodies do not have a substantial clinical benefit as monotherapy and need to be combined with other checkpoint molecules for stronger immune responses.[50].

MBG543, a humanized IgG4 monoclonal antibody which blocks binding of TIM-3, was tested in combination with spartalizumab in phase 2 dose expansion in patients pretreated with anti–PD-1/L1 therapy with NSCLC and melanoma.[51] Among the 17 patients with NSCLC, 2 (11.8%) had ongoing response while most progressed. On prior anti–PD-1/L1 therapy, 41.2% patients had durable clinical benefit. This study established the tolerance of MBG543 with spartalizumab however there was limited efficacy. Currently, many other anti-TIM3 agents are currently in development, whose results are eagerly awaited.

Anti-PD-1/PD-L1 and Anti-GITR

Glucocorticoid Induced TNF-related Receptor (GITR) is a co-stimulatory TNF receptor super family member constitutively expressed in regulatory T cells (Treg) and upregulated upon T cell activation in effector T cells (Teff).[52] Thus, it affords the potential to expand $CD8^{+}$ Teff memory cell population while promoting the loss or inhibition of Tregs.[53] A GITR targeting antibody should then shift the balance in the $CD8^{+}$ Teff/Treg ratio to impart robust antitumor immunity.

BMS-986156 is an IgG1 agonist monoclonal antibody to GITR, which was designed to increase T-cell activation and deplete intratumoral regulatory T cells in combination with anti-PD-1 therapy.[54] This was tested in a phase 1/2a study as monotherapy treatment and in combination with nivolumab in patients with advanced solid tumors. Overall, the safety profile of BMS-986156 was tolerable, with treatment related adverse event occurring in 2.9% in monotherapy arm and 5.4% in combination arm. BMS-980156 showed no single agent activity (ORR:0%), with improved activity in combination with nivolumab (ORR: 1.0–11.1%). Within the subset of NSCLC patients (n = 37), the combination of BMS-980156 and nivolumab showed modest activity with disease control rate (DCR) of 40.5% and ORR of 2.7%, when most patients had received prior anti-PD-1/PD-L1 therapy. Unfortunately, similar modest to no anti-tumor activity was demonstrated with other anti-GITR compounds including AMG228[55], MEDI1873[56], and GWN323[57] either as monotherapy or in combination with other anti PD-1/PD-L1 inhibitors.

Anti-PD-1/PD-L1 and Anti-NKG2A

NKG2A, a cell-surfaced expressed lectin-type novel immunomodulatory checkpoint molecule, is constitutively present on NK cells or inducibly expressed on CD8 T cells.[58] NKG2A forms heterodimers with the CD94 chain[59] and recognizes the nonclassical HLA class I molecule HLA-E.[60] Studies demonstrate high expression of NKG2A on NK cells and cytotoxic CD8 T cells in the tumor microenvironment as a result of PD-1 blockade therapy.[61] Hence, targeting NKG2A in combination with currently available anti-PD-1/PD-L1 antibodies may be an exciting strategy to increase responses.

Monalizumab is a humanized IgG4 antibody blocking the interaction of human NKG2A with HLA-E.[62] Although, monalizumab monotherapy was shown to have limited single agent activity[63], its combination with durvalumab is under investigation in multiple tumor types (NCT02671435). For NSCLC, monalizumab has been tested in both the neoadjuvant and unresectable Stage III setting. The NeoCOAST platform study evaluated neoadjuvant durvalumab in combination with novel immunotherapy agents including monalizumab with the primary objective of evaluating Major Pathologic Response (MPR) rate.[64] The study showed that novel immunotherapy combinations with anti-CD73 monoclonal antibody oleclumab (19%), anti-NKG2A monoclonal antibody monalizumab (30%) and anti-STAT-3 monoclonal antibody danvatirsen (31%) increased MPR rates compared to durvalumab alone (11%). These encouraging results have resulted in launch of a randomized study of neoadjuvant and adjuvant treatment with novel immunotherapies in the NeoCOAST-2 trial (NCT05061550). The COAST trial evaluated durvalumab alone or combined with the oleclumab or monalizumab as consolidation therapy in unresectable stage III NSCLC, building upon the standard of durvalumab consolidation from the PACIFIC trial.[65] This phase 2 study demonstrated improved ORR (35.5% vs. 17.9%) and PFS with durvalumab in combination with monalizumab compared to durvalumab alone (15.1 vs. 6.3 months, HR: 0.42; 95% CI, 0.24 to 0.72). Given this early success for targeting NKG2A in NSCLC, there could possibly be a role for utilization of these therapies in with other immunotherapy agents in mNSCLC. PACIFIC-9 (NCT05221840) is currently assessing effects of durvalumab with monalizumab or oleclumab following concurrent chemoradiation in patients with stage III unresectable NSCLC.

Anti-PD-1/PD-L1 and adenosine receptor antagonists

Targeting the adenosine pathway given the inhibitory role of adenose in anti-tumor immune responses is of increasing interest. Two potential strategies of interest in blocking the adenosine pathway is targeting CD73 (blocking production) and adenosine receptors A2AR (blocking signaling).[66] Multiple CD73 antagonists and A2AR antagonists are currently in development of which a few have been studied in NSCLC including oleclumab (CD-73 antagonist, MEDI-9447), ciforadenant (A2AR antagonist, CPI-444) and etrumadenant (A2AR antagonist, AB928). Oleclumab showed improved MPR in neoadjuvant setting [64] and median PFS in Stage III unresectable setting[67] when combined with durvalumab compared to durvalumab alone, as previously described. Ciforadenant was studied in the MORPHEUS-NSCLC phase 1B/2 open label randomized study combining atezolizumab with ciforadenant showing no significant improvement in median PFS (2.3 vs 3.2 months, HR:1, 95% CI: 0.4–2.3).

Anti-PD-1/PD-L1 and Anti-CD38

CD38, a multifunctional cell surface protein with receptor and enzymatic function, is expressed at low levels in various hematological and solid tissues. Meanwhile, plasma cells express particularly high levels of CD38, enabling development of various therapeutic CD38 antibodies, including daratumumab, isatuximab, and MOR202 for use in multiple myeloma.[68] In solid tumors, CD38 contributes to the tumorigenic properties of the TME. It is one of the three ectoenzymes involved in the production of adenosine, suppressing the activity of cytotoxic T cells, reducing their proliferation, cytokine production, and killing capacity - leading to evaluation of anti-CD38 therapies in solid tumors.[69].

A phase 1b/2 randomized study evaluated the safety and efficiency

of daratumumab plus atezolizumab versus atezolizumab alone.[70] In this study, the ORR was 4.3% for daratumumab plus atezolizumab, but 13.0% for atezolizumab alone. Furthermore, no improvements in median PFS or median OS was seen for the combination therapy. Another anti-CD38 and anti-PD-1 antibody combination studied was isatuximab combined with cemiplimab in the LUC2001 trial. The combination of these two antibodies showed a concerning safety profile with 60% Grade $\geq$ 3 adverse events and in patients with NSCLC.[71] In terms of efficacy for NSCLC, no CR or PR, but 65% stable disease (SD) rate was seen with the combination. Post therapy translational evaluation demonstrated that the combination led to reduction in CD38 + tumour-infiltrating immune cell but no consistent modulation of PD-L1.

Given the modest responses with CD38-targeting antibodies in non-hematopoietic solid malignancies including NSCLC, further ongoing explorations and clinical trials are needed to clarify the appropriate combinations and signatures for the application of CD38 in solid malignancies.[72].

Immunotherapy and targeted therapies

The immunosuppressive effect of VEGFR signalling on tumor microenvironment (TME) has been described>20 years ago, with more recent data demonstrating its additional role in immune checkpoint inhibitor resistance.[73,74] Specifically, tumor angiogenesis induces local hypoxia and recruits immunosuppressive cells, whereas hypoxia subsequently promotes tumor angiogenesis. Since efficacy of immunotherapy depends on the accumulation and activity of tumor-infiltrating lymphocytes, combining it with antiangiogenic therapy could improve local perfusion, relieve tumor microenvironment hypoxia, and reverse the immunosuppressive state. [75].

Vascular endothelial growth factor (VEGF) released by tumor cells inhibits T-cell responses and induces proliferation of Tregs and myeloid derived suppressor cells (MDSCs).[76] Another important component of TME is the TAM family of receptor tyrosine kinases (RTKs) which includes Tyro3, Axl, and MerTK receptors. [77] AXL, MER and Tyro3 inhibit pro inflammatory cytokines and stimulate immunosuppressive cytokines while MER also inhibits polarization of macrophages from M1 (immune stimulating) to M2 (immunosuppressive) subtype.[78] Given the strong pre-clinical rationale of augmentation of immune checkpoint inhibitor response[79], successful combinations in other tumor types [80] and approval of anti-VEGF monoclonal antibodies in treatment of non-mutated [81,82] and EGFR-mutated NSCLC[83]; combination immunotherapy and tyrosine kinase inhibitors are currently an area of active investigation.

Ramucirumab, an intravenous monoclonal antibody, which acts by blocking activation of VEGFR-2 is currently approved for use in patients for use in combination with docetaxel for the treatment of patients with mNSCLC with disease progression on or after platinum-based chemotherapy.[82] Recently, the phase 2 Lung MAP S1800A trial evaluated the combination of ramucirumab and pembrolizumab in patients previously treated with platinum-based chemotherapy and immunotherapy (with progressive disease at least 84 days after initiation of immunotherapy). This was compared with standard of care (SOC) which included either docetaxel/ramucirumab, docetaxel, gemcitabine and pemetrexed. Although the overall response rates and median PFS was comparable between 2 arms there was an improvement in overall survival with ramucirumab/pembrolizumab (14.5 versus 11.6 months, HR:0.69 [0.51 to 0.92]; p = 0.05) Grade>= 3 treatment-related adverse events occurred in 42% in the experimental arm compared to 60% on SOC.[84] Another phase 2 study of atezolizumab with bevacizumab for non squamous NSCLC with high PDL1 expression demonstrated an ORR of 64%, demonstrating combination of immunotherapy with anti-VEGF can be used in first-line treatment.[85].

Several multi tyrosine kinase inhibitor oral targeted therapies are also currently under study in combination with immunotherapy in the post immunotherapy progression setting. Three such studies that have been reported include combination of cabozantinib with atezolizumab (COSMIC-021) [86], sitravatinib and nivolumab (MRTX-500)[87], pembrolizumab and lenvatinib (LEAP 007)[88].

COSMIC-201, a multicenter phase 1b study, evaluating the combination of cabozantinib and atezolizumab in various solid tumors. Cohort 7 specifically reported outcomes in NSCLC showing ORR 19% in overall population with mDOR 5.8 months (4.2, 6.9). The median PFS and OS were 4.5 and 13.8 months respectively. Treatment discontinuation rates were 16% with 26% patients experiencing grade 3–4 toxicity.[86] Recent press release data reported negative results of the phase III CONTACT-01 trial evaluating cabozantinib in combination with atezolizumab in patients with metastatic NSCLC previously treated with immunotherapy and chemotherapy, which did not meet its primary OS endpoint.[89].

MRTX-500, a multicenter phase 2 study, evaluating the combination of sitravatinib and nivolumab in patients with nonsquamous NSCLC with prior clinical benefit from immunotherapy.[90] Results demonstrated ORR 18% in overall population with mDOR 12.8 months. The median PFS and OS were 5.7 and 14.9 months respectively. This regimen was found to be quite toxic with 66% patients experiencing grade 3–4 TRAEs, leading to discontinuation in 22% of patients. Treatment discontinuation rates were 16% with 26% patients experiencing grade 3–4 toxicity. A phase 3 study, SAPPHIRE (NCT03906071) is evaluating this combination in comparison to docetaxel in advanced NSCLC.

Finally, combination of pembrolizumab and lenvatinib was evaluated in the LEAP program. Results from the phase 3 LEAP-007 investigated the efficacy and safety of pembrolizumab with or without lenvatinib in adults with PD-L1-positive treatment-naïve NSCLC. Eligible patients (n = 623) were randomized 1:1 to receive either pembrolizumab plus oral lenvatinib (20 mg daily) or pembrolizumab plus placebo.[91] The primary endpoint included PFS according to RECIST v1.1 and OS, while secondary endpoints enclosed ORR, safety, QoL and patient-reported outcomes (PROs). The median OS was not improved with the combination therapy (14.1 vs 16.4 months (HR, 1.10; p = 0.79744)), despite the median PFS was reached (6.6 vs 4.2 months (HR, 0.78; p = 0.00624)) and improvement in ORR (40.5% vs 27.7%). After a median duration of treatment of approximately 6 months, pembrolizumab plus lenvatinib was associated with higher rates of grade 3–5 treatment-related adverse events (TRAEs) (57.9 vs 24.4 %), as well as AEs leading to discontinuation or death, compared with pembrolizumab alone. Further phase III studies evaluating pembrolizumab plus lenvatinib in NSCLC patients are ongoing comparing this combination with chemoimmunotherapy in LEAP-006 (NCT03829319) and docetaxel in LEAP-008 (NCT03976375).

Novel immunotherapy approaches

Many other novel approaches are being identified and combined with anti PD-1/PD-L1 blockade given its ability to enhance antitumor immunity. Combination of these agents with cancer vaccines, cytokine inhibition, radiation therapy and DNA damage response inhibitors have been tried with many studies currently under investigation.

Anti-PD-1/PD-L1 and vaccines

Given that tumor antigen/HLA related changes is an established mechanism of primary and acquired immunotherapy resistance, cancer vaccines can plan important role in generation of antitumor immune response through activation or priming of naïve antigen specific T-cells by antigen presenting cells, thus enabling amplification of tumor specific T-cell responses.[92].

Although previous phase 3 studies with peptide (Tecemotide, MAGE-A3)[93,94] and whole cell (belagenpumatucel)[95] vaccines did not show any activity for NSCLC in either adjuvant or metastatic setting, the advent of immune checkpoint blockade has reinvigorated interest in

cancer vaccines in combination with approved anti-PD-1/PD-L1 agents. With faster and cheaper availability of next generation sequencing and refined informatics prediction tools for identification of new antigens, personalized neoantigen vaccines to target patient specific antigens and inducing long-lasting tumor specific memory T cells are a highly desirable possibility.[96] A phase 1b trial of NEO-PV-01 peptide vaccine was recently reported demonstrating safety and immunogenicity of this vaccine in combination with nivolumab, leading to an ORR of 39% and median PFS of 8.5 months in patients with NSCLC (n = 18).[97].

ATALANTE-1 was a randomized, open-label, phase III study comparing the efficacy of Tedopi® with SOC in HLA-A2 positive patients with advanced NSCLC after progression on immunotherapy.[98] Many trial design and statistical plan modifications were successively applied during the trial conduct. The presented exploratory dataset focused on a population of interest, defined as secondary resistance to sequential chemotherapy and immunotherapy – a population not encountered today based on standards of care, was suggesting some activity of Tedopi®..[99].

Anti-PD-1/PD-L1 and cytokines

Cytokines, such as high dose recombinant IL-2 was one of the earliest immunotherapies studied in patients with advanced cancers.[100] Since then, many other cytokine based therapies have been tried in NSCLC including IL-1ß, IL-10, IL-15 and adenosine pathway based therapies.

The phase 3 CANTOS trial evaluated canakinumab, a monoclonal antibody binding to IL-1ß in secondary prevention of cardiovascular events and identified up to 67% reduction in lung cancer incidence-prompting further evaluation of this drug in NSCLC.[101] However, two focused phase 3 trials in second-line (CANOPY-2) and first-line (CANOPY-1) treatment of mNSCLC did not demonstrate any significant improvement over current standard of care therapies.[102] More recently, studies evaluating canakinumab in early stage NSCLC with the CANOPY-N[103] evaluating canakinumab with or without pembrolizumab in Stage I-IIIA NSCLC in the neoadjuvant setting and CANOPY-A[104] evaluating canakinumab in resected Stage IIA-IIIB in the adjuvant setting failed to reach their MPR and DFS endpoints respectively.

Pegilodecakin (pegylated IL-10) is a first-in-class, long-acting IL-10 receptor agonist that induces oligoclonal T-cell expansion with single agent activity in solid tumors[105] and manageable toxicity profile when combined with anti-PD-1/PD-L1 immunotherapies.[106] CYPRESS-1 and CYPRESS-2 were two randomized phase 2 studies evaluating combination of pegilodecakin with pembrolizumab (CYPRESS-1) in first line and with nivolumab (CYPRESS-2) in second line mNSCLC. Both these studies were negative and did not show any improvement compared to single agent anti PD-1/PD-L1 regardless of PD-L1 expression levels.[107] A phase 1b study evaluated ALT-803, an IL-15 super agonist in combination with nivolumab in patients with mNSCLC demonstrating safety and efficacy with ORR of 29%.[108].

Anti-PD-1/PD-L1 and PARP inhibitors

Based on encouraging preclinical data demonstrating cross-talk between PARP inhibitor (PARPi) and tumor-associated immunosuppression, combination of PARPi and anti PD-1/PD-L1 antibody is being studied as a potential therapeutic approach.[109] This combination has been tested in the first-line setting in the phase 2 JASPER trial and a phase 1 trial combining PARP inhibitor with chemoimmunotherapy. The phase 2 JASPER trial studied niraparib in combination with pembrolizumab in 38 patients with OR of 56.3% and 20% and median PFS of 8.4 and 4.2 months in patients with TPS >=50% and 1–49% respectively.[110] Clarke et al. studied the safety and efficacy of combination of veliparib with nivolumab, carboplatin and paclitaxel/pemetrexed and found that among 25 patients enrolled in this study, the ORR was 40% with no DLTs.[111] Currently, trials are ongoing not only for other PARP inhibitors such as olaparib (ORION: NCT03775486, KEYLINK-006: NCT03976323, KEYLINK-008: NCT03976362), niraparib (ZEAL-1L: NCT04475939) and talazoparib (NCT03330405) but also other DNA damage repair based inhibitors such those that target the ATR (ataxia telangiectasia mutated and Rad3-related) kinase (cerlasertibin HUDSON study (NCT03334617), berzosertib in NCT04216316) in combination with anti-PD-1/PD-L1 agents.

Anti-PD-1/PD-L1 and radiation therapy

Radiation therapy has been one of the major pillars of cancer therapy. It has been observed in a limited number of case reports, mainly in melanoma, that immune mediated response to radiation distant from the irradiated site, also known as “abscopal effect”, may improve outcomes in metastatic disease.[112] The advent of anti PD-1/PD-L1 immunotherapy has reinvigorated interest in this phenomenon given the non-redundant immune synergy between radiation and immunotherapy.[113] With the focus of improving outcomes for patients who do not respond to immunotherapy, efforts have been aimed at combining immunotherapy and radiotherapy.

PEMBRO-RT trial evaluated combination of radiotherapy with pembrolizumab compared to pembrolizumab alone in advanced NSCLC. No difference in response rates were noted with the combination treatment (36% vs 18%; p = 0·07).[114] Another trial conducted at MD Anderson Cancer Center tested administration of pembrolizumab with radiation therapy, demonstrating no differences in outcomes between combination versus immunotherapy alone (median PFS 9.1 vs 5.1 months, p = 0.52).[115] although statistically not significant, there were clinically notable difference in response rates and outcomes in the combination treatment, thus leading to a pooled analysis of these 2 randomized trials. The pooled analysis demonstrated improvement in overall survival with combination treatment having median overall survival of 19.2 months compared to 8.7 months with immunotherapy alone (HR:0.67, p = 0.0004).[116].

Another study evaluated combination of radiation therapy with dual PD-L1 and CTLA-4 blockade (with durvalumab and tremelimumab). This trial conducted by NCI ETCTN was randomized phase 2 trial comparing 3 groups: Durvalumab and tremelimumab alone, durvalumab and tremelimumab plus low-dose radiotherapy, and durvalumab plus tremelimumab plus hypofractionated radiotherapy. Unfortunately, this trial was stopped due to futility assessed in an interim analysis where no difference in overall response rates were observed between the 3 groups.[117] Given the conflicting results in different trials, this approach continues to need further evaluation with ongoing trials in this space.

Conclusions

In conclusion, several immuno-oncology targets and combinations are currently being studied, including those for the management of mNSCLC. However, in order to truly advance and improve outcomes for patients with mNSCLC, we need better biomarker driven studies which can harness our understanding of immuno biology and etiology of deficits in antitumor response at an individual level.[6] This is currently being implemented through design of multi-arm platform trials which aim to provide deeper understanding of resistance to current immune checkpoint inhibitors and identification of biomarkers to evaluate novel therapies (PIONeeR)[118] or provide biomarker matched and non-matched treatment for patients resistant to both chemotherapy and immunotherapy treatments (HUDSON).[119] In fact, the HUDSON platform results have supported an ongoing phase 3 trial comparing durvalumab and ceralasertib with docetaxel (NCT05450692).

The most recent report of KEYNOTE-495/KeyImPaCT study demonstrated the feasibility of designing biomarker driven immunotherapy trials in patients with previously untreated NSCLC.[120] Based on T cell gene expression profiles and tumor mutation burden, patient

were divided into 4 different subgroups and randomized to different treatment arms which included pembrolizumab + lenvatinib, pembrolizumab + quavonlimab (anti-CTLA-4), and pembrolizumab + favezelimab (anti-LAG-3). Pembrolizumab + lenvatinib treatment met prespecified efficacy bar in his specific subgroup of patients while other arms did not meet the prespecified efficacy criteria in any dual biomarker-based subgroup.

However, this study provides proof of concept that prospective biomarker-based immunotherapy trials are feasible and should be the way forward for immunotherapy over the next decade. Successful combinations and smartly designed studies would require improved patient selection for a much needed a "precision immunotherapy" approach to identify the right dose of the right immunotherapy combination, for the right patient, at the right time.

CRediT authorship contribution statement

Aakash Desai: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Solange Peters:** Conceptualization, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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