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Emerging Therapies in Thoracic Malignancies—Immunotherapy, Targeted Therapy, and T-Cell Therapy in Non–Small Cell Lung Cancer

Boris Sepesi, MD,*, Tina Cascone, MD, PhD, Stephen G. Chun, MD, Mehmet Altan, MD, Xiuning Le, MD

INTRODUCTION

Over the past decade there have been dramatic therapeutic advances for non–small cell lung cancer (NSCLC) that have been based on an improved understanding of biomarkers, tumor immunology, driver mutations, T-cell receptors (TCRs), and adoptive immune therapies. As a result of these advances, the overall survival (OS) currently seen with immunotherapy and targeted biologic regimens is remarkably longer than with historic cytotoxic chemotherapy. These discoveries have created many new

KEYWORDS

- Immunotherapy
- Targeted therapy
- T cells
- Adoptive therapy
- Non–small cell lung cancer

KEY POINTS

- Immunotherapy has improved survival and advanced treatment options for metastatic non–small cell lung cancer, and it is being actively studied in local and regional lung cancer settings.
- Cancer gene mutations and alterations provide a significant opportunity for the development of targeted agents, which have been very successful in cancer control and survival outcomes.
- Adoptive T-cell therapies are promising new therapeutic options for solid cancers, including lung cancer, although more research and trials are needed in this space.

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* Corresponding author. Department of Thoracic and Cardiovascular Surgery, The MD Anderson Cancer Center, 1400 Pressler Street, FCT. 196004, Unit 1489, Houston, TX 77030-4009.
E-mail address: bsepesi@mdanderson.org

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possible therapeutic options for lung cancer patients in both local and metastatic settings. This article reviews the current landscape of immunotherapy, targeted therapy, and adoptive therapy in NSCLC.

IMMUNOTHERAPY IN NON–SMALL CELL LUNG CANCER

Arguably, the most important paradigm-changing innovation for NSCLC of the past decade has been the advent of anti–programmed death cell protein-1 (PD-1) and anti–programmed death ligand 1 (PD-L1) as well as cytotoxic T-lymphocyte–associated protein 4 (CTLA-4)–directed immune checkpoint blockade (ICB). ICB therapy is based on the recognition that tumors express PD-L1 to evade the immune system by suppressing T cells by binding the PD-1 transmembrane receptor. In turn, the utilization of targeted antibodies to perturb PD-1/PD-L1 signaling has proved to have remarkable antitumor activity in NSCLC. Currently, there are 2 anti–PD-1 and 1 anti–PD-L1 agents that are approved by the Food and Drug Administration (FDA) for the treatment of metastatic NSCLC and 1 anti–PD-L1 antibody in the consolidative setting after concurrent chemoradiation for locally advanced NSCLC. Depending on the tumor PD-L1 expression level, ICBs can be utilized either as monotherapy or in combination with chemotherapy in the first-line setting for metastatic NSCLC. This article reviews seminal phase III trials utilizing anti–PD-1 agents nivolumab and pembrolizumab and anti–PD-L1 agent atezolizumab in metastatic NSCLC.

The initial phase III trials, which demonstrated the benefit of immunotherapy in metastatic NSCLCs, tested the anti–PD-1 antibody nivolumab in the second-line setting after recurrence or progression on cytotoxic chemotherapy. These trials included CheckMate 017 in squamous NSCLC and CheckMate 057 in nonsquamous cell lung carcinomas. Both trials demonstrated better OS with nivolumab compared with docetaxel alone and received FDA approval as the second-line therapy. Based on these encouraging results, nivolumab was added to the platinum-doublet chemotherapy in the first-line setting in the CheckMate 026 trial, in the hope of improving survival outcomes over standard chemotherapy. This trial did not reach the primary endpoint, however, of improved progression-free survival (PFS) or OS, suggesting that nivolumab may not enhance outcomes when combined with platinum-doublet therapy.

In the CheckMate 227 trial, nivolumab was combined with anti–CTLA-4 antibody ipilimumab, and compared in the first-line setting against standard chemotherapy; dual ICB therapy previously demonstrated encouraging results in metastatic melanoma. The trial stratified patients based on tumor PD-L1 expression. Results in patients with PD-L1 greater than 1% demonstrated significantly longer median OS with ICB combination compared with chemotherapy. The efficacy of pembrolizumab was studied in the KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, and KEYNOTE-407 phase III trials and further corroborated the benefit of ICB for metastatic NSCLC. Importantly, KEYNOTE-024 established pembrolizumab as the first-line ICB monotherapy in wild-type epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase, metastatic NSCLC with PD-L1 expression greater than or equal to 50%. KEYNOTE-042 expended on pembrolizumab indications by demonstrating benefit even in patients with PD-L1 greater than 1%. KEYNOTE-189 and KEYNOTE-407 studied combination of pembrolizumab and chemotherapy in all-comers in nonsquamous and squamous cell lung carcinoma, respectively; survival outcomes were favorable with pembrolizumab in both trials.
These studies secured the indications for pembrolizumab alone or in combination with chemotherapy in the first-line metastatic NSCLC. Atezolizumab is a monoclonal antibody directed against PD-L1 and was studied in IMPower 110 (NCT02409342), IMPower 150, IMPower 130, IMPower 131 (NCT02367794), and IMPower 132 (NCT02657434) trials. IMPower 110 (NCT02409342), similarly to KEYNOTE-042, demonstrated survival benefit with monotherapy compared with chemotherapy in patients with PD-L1 greater than or equal to 1%. In IMPower 150 trial, atezolizumab, chemotherapy, and bevacizumab resulted in improved survival, even in EGFR-positive patients. IMPower 130 showed benefit of atezolizumab in combination with chemotherapy in the first-line metastatic nonsquamous lung cancer without EGFR or ALK mutations, whereas IMPower 131 (NCT02367794), and IMPower 132 (NCT02657434) studied all-comers with metastatic squamous and nonsquamous lung cancer, respectively. Survival benefit of atezolizumab added to chemotherapy regimen was evident in both histologies; therefore, atezolizumab alone or in combination with chemotherapy is indicated in the first-line metastatic NSCLC setting.

Currently, an area of controversy and active investigation in metastatic NSCLC is the role of local consolidative therapy (LCT). Although 2 randomized phase II trials have demonstrated an improvement in PFS with LCT for oligometastatic NSCLC treated with cytotoxic chemotherapy, this paradigm has yet to be validated in patients treated with ICB. Currently, the role of LCT for oligometastatic NSCLC treated with ICB is being tested in the context of multiple prospective clinical trials, including NRG Oncology-LU002 (NCT03137771) and the LONESTAR Trial (NCT03391869).

In summary, the advent of anti–PD-1/PD-L1 ICB has yielded major improvements in metastatic NSCLC outcomes. Current efforts to understand mechanisms of ICB resistance and the role of LCT are anticipated to further refine and improve patient care.

**Immunotherapy in Locoregionally Advanced Unresectable Non–Small Cell Lung Cancer**

Stage III NSCLC is a complex and heterogenous disease state, which historically has been the subject of much controversy regarding the most optimal therapeutic algorithms. Stage III generally includes either large tumors or centrally located tumors abutting or invading the mediastinum and/or cancer involved mediastinal lymph nodes, either single or multiple, or above the clavicle, which maybe bulky or nonbulky. Adding to this heterogeneity, a surgeon’s judgment of what constitutes resectable and unresectable disease along with options of induction chemotherapy or chemoradiation versus definitive concomitant chemoradiation creates numerous possible treatment algorithms and sequences. For patients deemed to have unresectable disease, concurrent chemoradiation has been the standard of care for decades without significant improvements in survival since the 1990s. The PACIFIC trial changed this paradigm. The PACIFIC trial enrolled surgically unresectable patients and randomized them to chemoradiation with or without 1 year of consolidative durvalumab. Initial results from this trial demonstrated improved PFS. Subsequent OS analyses revealed improved OS of 83%, 74%, and 66% at 1 year, 2 years, and 3 years, respectively, all 10% to 20% better than with chemoradiation alone. These results prompted FDA approval of durvalumab for stage III locally advanced NSCLC. How to further improve on these results and what to do in surgically resectable stage III NSCLC is an area of continuous study. Adjuvant durvalumab mainly improved rates of metastatic disease, including brain metastases that occurred at rates of less than 5%, which was dramatically lower than historic brain metastasis rates for stage III disease. What the rates of locoregional disease control are with this regimen is not totally
clear; would trimodality therapy with concurrent chemoradiation and surgery further improve local control, and in turn survival? It also has been postulated that lower immune-priming doses of radiation might result in neoantigen activation and help prevent distant recurrence with surgical locoregional control to account for lower radiation dose. Would concomitant administration of radiation and durvalumab be even more effective? These, and many other questions remain unanswered and are tested in ongoing clinical studies.

**Immunotherapy in Local and Locoregionally Advanced Resectable Non–Small Cell Lung Cancer**

Currently, there are no approved immunotherapy regimens as part of the standard of care in the perioperative setting for surgically resectable NSCLCs. There are, however, numerous ongoing clinical trials testing the efficacy of mono or dual immunotherapy regimens as well as the combinations of immunotherapy and chemotherapy in the neoadjuvant setting.

**Neoadjuvant Monoimmunotherapy**

The first trial testing neoadjuvant ICB enrolled 21 patients with resectable stages IB–IIIA NSCLC.18 Patients received 2 doses of neoadjuvant nivolumab followed by surgery. The aims of the trial were safety and feasibility of surgical resection within 4 weeks of the 1st dose of nivolumab, which were met. The secondary endpoint of major pathologic response (MPR) was 45% and downstaging was achieved in 40% of patients after just 2 therapeutic doses.18 The Lung Cancer Mutation Consortium (LCMC) 3 study19 targeted accrual has been 180 patients; preliminary results showed that 2 doses of neoadjuvant atezolizumab induced 19% MPR rate and 5% of evaluable patients achieved pathologic complete response. These results overall are similar to the MPR after 3 cycles of nivolumab in the phase 2 randomized NEOSTAR (NCT03158129) trial,20 which demonstrated MPR of 17% in 23 treated patients. In another neoadjuvant study evaluating PD-1 inhibitor sintilimab in resectable NSCLC, 2 doses of neoadjuvant ICB induced 40.5% MPR rate,21 which is similar to the results of phase I study MK3475-223 (NCT02938624)22 with pembrolizumab (MPR 40%). Although there is a clear intertrial variability in terms of MPR rates after ICB monotherapy, which may be driven by several variables, including the type of immunotherapy, tumor histology, oncogenic drivers, and perhaps number of doses prior to surgery, it appears that neoadjuvant anti–PD-1/PD-L1 therapy is overall safe and feasible and its efficacy appears to be very similar or slightly better than platinum doublet chemotherapy.

**Neoadjuvant Dual Immunotherapy**

The combination of nivolumab and ipilimumab in the neoadjuvant setting has been studied in 2 phase II trials (NEOSTAR [NCT03158129 and NCT02259621]). Recently reported results from the NEOSTAR trial investigating nivolumab given with 1 dose of ipilimumab suggested that the combination is overall well tolerated and induced 33% MPR rate. The results of NCT02259621 have not yet been presented; the trial plans to accrue 30 patients. Whether dual immunotherapy will be tested further in larger studies is currently unclear and likely depends on translational analyses from these trials, which may help identify sounds of patients responding to this therapy. Although MPR rates with dual ICB appear to be improved compared with MPR with neoadjuvant chemotherapy (15%–19%), the unprecedented MPR rates achieved after combination of immunotherapy and chemotherapy most likely will play the leading role in advancing the neoadjuvant NSCLC field forward.
Several ongoing trials are investigating the paradigm of neoadjuvant combined anti-PD-1/PD-L1 inhibitors with chemotherapy for resectable NSCLC patients. The NADIM trial\(^{23}\) is a single-arm phase II trial, which administered 3 doses of chemotherapy along with nivolumab prior to resection of clinically staged IIIA NSCLC. The trial enrolled 46 patients, and 89% had clinical N2 disease, majority (75%) multistation. Resectability was 89% (41/46). Importantly, the trial reported an unprecedented MPR response rates of 83% (in resected 41 patients, or 73% (34/46) if analyzed by the intention to treat). Complete pathologic response was reported in 24 patients; OS at 18-month follow-up was 91%. These results are remarkable, but require validation in currently ongoing phase III trials in order to definitively change practice paradigm for neoadjuvant therapy in NSCLC. Notable ongoing phase III trials include CheckMate 816 (NCT02998528)\(^{24}\) utilizing nivolumab with chemotherapy, and randomized phase III trials: KEYNOTE-671 (NCT03425643, pembrolizumab), IMpower 030\(^{25}\) (NCT03456063, atezolizumab), AEGEAN\(^{26}\) (NCT03800134, durvalumab), and CheckMate 077 (NCT04025879, nivolumab); these randomized trials will compare combined immune-chemotherapy to standard neoadjuvant chemotherapy. All are either excluding or carefully stratifying patients with targetable somatic oncogenic drivers.

Randomized phase III trials will potentially bring the combined neoadjuvant immune-chemotherapy into the realm of standard of care if they will achieve results close to the NADIM trial.

**TYROSINE KINASE INHIBITORS AND TARGETED THERAPY**

**Targeted Therapy in Metastatic Lung Cancers**

The stratification of NSCLC with molecular oncogene alterations has changed the treatment paradigm and meaningfully improved patients’ survival and the quality of life.\(^{27}\) A driver oncogene can be detected in two-thirds of adenocarcinomas. There are 5 oncogenes in NSCLC with FDA-approved targeted therapies for metastatic diseases, and many others are anticipated to be added to the clinical armamentarium.

The first actionable mutations in NSCLC have been EGFR mutations. In 2004, 3 groups identified tumors harboring EGFR exon19 deletion or exon21 L858R mutations that were exquisitely responsive to EGFR tyrosine kinase inhibitors (TKIs).\(^{28–30}\) In metastatic setting, it was shown that the treatment with EGFR inhibitor can improve patients’ PFS and quality of life compared with chemotherapy.\(^{31–33}\) Although EGFR mutations are more prevalent in Asian female never-smoker patients (up to 65%), it also occurs in patients with other demographic features. Therefore, it has been recommended that all newly diagnosed metastatic NSCLC be tested for mutations in this gene. With erlotinib or gefitinib (first-generation EGFR TKIs), approximately half of the EGFR-mutant tumors acquire a new EGFR mutation T790M to displace drug binding out of the EGFR adenosine triphosphate pocket and render clinical resistance to treatment.\(^{34}\) To overcome this type of resistance, newer EGFR inhibitors were designed, such as osimertinib.\(^{35}\) In AURA trials, osimertinib was able to confer response in T790M tumors after progression on erlotinib or gefitinib.\(^{36}\) Furthermore, in newly diagnosed metastatic patients, osimertinib was associated with better PFS\(^{37}\) and OS.\(^{38}\) Osimertinib currently is the preferred first-line choice for metastatic NSCLC with EGFR sensitizing mutations, with other 4 EGFR TKIs serving as alternative options.

ALK-rearranged NSCLC is another prime example of targeted therapy. It took only 3 years from discovering that ALK fusion with ELM4 is a driver fusion for NSCLC,\(^{39}\) to showing that crizotinib induces response in 57% of ALK-rearranged NSCLC.\(^{40}\) Similar
to EGFR TKIs, newer-generation ALK TKIs, such as ceritinib, alectinib, brigatinib, and lorlatinib, demonstrated better efficacy and the ability to overcome acquired ALK mutations. Currently, the OS for patients on ALK inhibitors extends beyond 5 years (6.8 years).

ROS1 is another kinase structurally very close to ALK. The fusion of ROS1 occurs in 1% to 3% of NSCLC. Not surprisingly, crizotinib, certinib, and lorlatinib all are active in ROS1-fusion NSCLC.

BRAF V600E mutation initially was recognized in melanoma and dual inhibition of MEK and RAF was established in melanoma as an effective therapeutic strategy. In a phase II study using dabrafenib plus trametinib in BRAF V600E NSCLC patients, response rate was 68%, with almost all patients experiencing tumor reduction. The FDA approved this combination based on this single-arm pivotal trial.

Most recently, NTRK inhibitors have demonstrated outstanding efficacy in tumors harboring NTRK1/2/3 fusions, regardless of the tumor type. In this study, in the lung cancer subgroup, 75% patients responded well to therapy. Thus, NTRK inhibitors became the newest addition to the therapeutic options for treating lung cancers with an oncogene driver.

In addition to the FDA-approved medications for the 5 different oncogenic alterations, new targets and therapies continue to emerge and some have shown promise in their early efficacy.

RET fusion as a target for NSCLC has been recognized since 2012. Several TKIs targeting ALK and ROS1, for example, alectinib, were found to have activities for RET-fusion.

METex14 skipping was identified as a potential oncogenic driver in 2015 to 2016. By splicing interruption with exon 14, c-MET signaling is constitutively active due to the lack of degradation. Small molecule inhibitors, such as crizotinib, tepotinib, capmatinib, and savolitinib, all demonstrated efficacy in NSCLC patients with METex14 skipping mutation. Two drugs, tepotinib and capmatinib, currently are under fast-track review with regulatory agencies around the globe for approval.

Other than classic mEGFR sensitizing mutations at exon 19 and exon 21 L858R, EGFR and HER2 exon20 insertions also are known oncogenic drivers. Many novel small molecule inhibitors are under development to target this population.

In 2019, the most exciting development in targeted therapy for NSCLC has been the observation of clinical efficacies with inhibitors targeting KRAS G12C. Many agents targeting KRAS and its pathways are under clinical evaluation now.

In summary, targeted therapies with precision medicine approach have revolutionized the treatment of metastatic NSCLC. The field is moving rapidly in several different directions. Aside from the continued effort in identifying new oncogenic drivers and the development of highly potent selective therapeutics, combination therapy with other classes of medications is being explored. Combination of targeted therapy with radiation or surgical LCT consolidation (NORTHSTAR [NCT03410043] and BRIGHTSTAR [NCT03707938] trials) also have shown initial success. Combinations with chemotherapy, antiangiogenics, ICB, and immune modulation agents all are under active investigation.

**Targeted Therapy in Resectable Stages I to III Non–Small Cell Lung Cancer**

Building on the success in metastatic NSCLC, clinical trials are evaluating targeted therapeutics in earlier stages, as adjuvant or neoadjuvant therapies. As adjuvant therapy, several trials evaluated EGFR inhibitors as adjuvant therapy after surgical resection of stages IB–IIIA NSCLC. The initial phase III RADIANT trial showed no disease-free survival (DFS) benefit for adjuvant erlotinib in patients with EGFR amplification,
but the subgroup of EGFR-mutant NSCLC favored erlotinib (median DFS, 46.4 months vs 28.5 months, respectively, with erlotinib vs without; \( P = .039 \)). In another randomized phase III Chinese study ADJUVANT-CTONG1104, 222 patients with N1-N2 disease (stages IIA–IIIA) were randomized to gefitinib for 2 years versus cisplatin/vinorelbine. The DFS was 28.7 months for gefitinib versus 18 months for chemotherapy; hazard ratio 0.60; \( P = .0054 \). The gefitinib group had more brain recurrence than chemotherapy group. In the United States, a similar adjuvant trial, Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) is a National Cancer Institute–sponsored National Clinical Trials Network initiative aiming at addressing the same question. ALCHEMIST screens patients with operable lung adenocarcinoma to determine if their tumors contain EGFR or ALK. Once the presence of EGFR or ALK is confirmed, patients are randomized to monitoring versus erlotinib or crizotinib, respectively, after completion of their standard adjuvant chemotherapy. Because osimertinib has an excellent anticancer activity for brain metastases, the field has been anxiously waiting for the results of the ADUARA trial, which administered osimertinib for 3-year after lung cancer resection. The data from this trial were announced via virtual 2020 American Society of Clinical Oncology meeting (due to COVID-19 pandemic). This phase III randomized trial of 682 patients was unblinded 2 years early after recommendations from an independent data monitoring committee due to 79% reduction in disease-free survival (DFS), defined as either recurrence or death, and 89% versus 53% 2-year DFS compared with placebo. This is a remarkable benefit of adjuvant osimertinib versus placebo in surgically resected patients with stages IB–IIIA EGFR positive adenocarcinoma.

In the neoadjuvant setting, data on targeted therapy are sparse, partially due to the challenge of obtaining mutational status prior to surgery. A coordinated effort with multiple large academic centers through LCMC is ongoing to address the question of whether neoadjuvant targeted therapy can improve patients’ outcome after surgical therapy. The current study, titled, “LCMC4: Screening Patients with Suspected Early-Stage Lung Cancers for Actionable Oncogene Targets,” is the fourth study conducted through the LCMC with the support of industrial and academic partners. The aim is to screen 1000 surgical patients for 10 actionable driver mutations (including EGFR, ALK, ROS1, and others). Patients with actionable mutations then will be enrolled on a mutation or alteration-specific neoadjuvant trials.

Although targeted therapy is not yet part of the standard of care in stages I–III NSCLC, the authors anticipate continued evolution of this field and incorporation of targeted therapy into future practice guidelines. The authors envision that rapid molecular testing and sequential or combination use of targeted therapy will help improve long-term outcomes in stages I–III NSCLC.

ADOPTIVE T-CELL THERAPIES, INCLUDING TUMOR-INFILTRATING LYMPHOCYTES THERAPY, CHIMERIC ANTIGEN RECEPTOR T CELLS, AND T-CELL RECEPTOR

The goal of cancer immunotherapy is to direct the immune system against tumor cells, leveraging its exquisite specificity and capacity for memory to achieve rapid and durable tumor clearance. Although clinical success of ICB in cancer has embraced this concept, these therapies benefit a fraction of all patients. The major barriers to efficacy include lack of preexisting tumor-specific T-cell response and exclusion of T cells from the tumor microenvironment. Adoptive T-cell therapies provide an opportunity to overcome these resistance mechanisms by infusion of large number of tumor antigen–specific cells into the host.
Tumor-Infiltrating Lymphocytes

In tumor-infiltrating lymphocytes (TILs) therapy, TILs are isolated from the tumor stroma, expanded ex vivo and reinfused peripherally after conditioning therapy. Nonmyeloablative lymphodepleting preparative regimen generally is given prior to lymphocyte infusion. This preconditioning therapy consists of cyclophosphamide and fludarabine, which enables dramatic increase and persistence of transferred cells in vivo, along with enhanced TILs antitumor activity. Lymphodepletion decreases regulatory T cells and myeloid-derived suppressor cells and provides homeostatic growth stimulus to adoptively transferred lymphocytes. TILs therapy application first was used in melanoma patients and induced responses in multiple melanoma studies. In other solid tumors, the identification and ex vivo culturing of TILs has been difficult. Although the diversity of T cells that provide broad nature of the T-cell recognition against both defined and undefined tumor antigens with this platform makes a strong argument for the utility of TIL therapies, challenges with quality and quantity of TILs remains its limitation. Efforts on optimizing the collection, expansion and preparation for TILs are ongoing to overcome some of these challenges. Number of studies in melanoma, including in patients with advanced melanoma who progressed on multiple prior therapies, including anti–PD-1 therapy, has shown promising clinical responses with this modality and led to subsequent registration studies. Experience in lung cancer with TILs therapies have been limited and currently pilot studies are ongoing to assess the utility of this approach.

Chimeric Antigen Receptors

Chimeric antigen receptors (CARs) are synthetic receptors that redirect the specificity, function and metabolism of T cells. CARs consist of T-cell activating domain and extracellular immunoglobulin derived heavy and light chains to direct specificity. These antibody fragments bind to specific antigens on the surface of cancer cells. Newer generations of CARs are engineered to express costimulatory receptors that can enhance proliferation and activation. CAR-based adoptive cellular therapies depend on an antibody like-mediated binding to the antigen and is independent from major histocompatibility complex (MHC) presentation. Advantages of CARs include the recognition of surface antigens independently from MHC restriction and antibody-like–mediated antigen recognition that allows targeting not only the cell surface proteins but also carbohydrates and glycolipids. Engineering of CAR molecules to obtain conditional activation or remote control of CAR T cells also provides additional advantages. In hematologic cancers, these applications provided significant therapeutic success in patient subsets, which led to the FDA approval of 2 CAR-engineered T-cell (CAR-T) therapeutic medicines. Tisagenlecleucel, the anti–cluster of differentiation 19 (CD19) CAR-T therapy, has been approved for the treatment of pediatric patients and young adults with refractory or relapsed B-cell precursor acute lymphoblastic leukemia. Another anti-CD19 CAR-T therapy, axicabtagene ciloleucel, was approved to treat adult patients with relapsed and refractory large B-cell lymphoma.

In solid tumors, the development of CAR-T therapy has been more challenging. CARs recognize only antigens expressed on the cell surface of tumor cells. These antigens are limited due to the overall tumor heterogeneity and nonuniformity of the antigen expression. Furthermore, potential target antigens often are shared between tumors and healthy normal tissue, which makes toxicity the main limitation. Few studies in thoracic malignancies showed feasibility of this platform. For
example, in mesothelin-associated malignant pleural solid tumors, primarily in malig-
nant mesothelioma, intrapleural administration of mesothelin-targeted CAR T cells in
combination with anti–PD-1 therapy after a preconditioning therapy with cyclophos-
phamide, showed evidence of CAR T-cell antitumor activity without therapy-related
major toxicity. In this study, with a minimum of 3 months’ follow-up, the best overall
response for a subset of 11 patients with malignant pleural mesothelioma was 72%,
including 2 durable complete metabolic responses and 6 partial responses. Nine of
these patients had PD-L1 less than or equal to 10%, and 6 of 8 responses were
seen in PD-L1–low patients. In another study, EGFR targeted CAR-T cells reported
2 partial responses and 5 stable disease for 2 months to 8 months in 11 evaluable
patients. CAR-T therapies have unique toxicities, such as cytokine release syn-
drome and neurotoxicity, which can be life threatening. Predictive algorithms have
been developed for the identification of these toxicities and supportive therapies.

T-Cell Receptor

The basic principle of T cell receptor gene therapy is to provide mature T lymphocytes
with a high affinity TCR; both alpha and beta chains. This approach is restricted to intra-
cellular peptides derived from tumor antigens and requires major histocompatibility
complex loading and surface presentation to allow immune synapse formation. Efforts
to confer durable, high-level T-cell modification largely have relied on genetic transfer
of TCR genes by integrating retroviral or lentiviral vectors.

The TCR-based gene therapy has certain advantages over some of the limitations
that have been faced with CAR-T therapies. TCRs can recognize not only cell surface
proteins but also any intracellular proteins. This allows TCRs to recognize low con-
centrations intracellular cognate antigens. In addition, the TCR approach mimics the
natural function of the T cell by recruiting the endogenous signaling molecules and
adhering to correct spatial orientation between the T cell and its target.

In this application, cancer testis antigens (CTAs) generally are selected as targets.
While selecting the targets, unexpected cross-reactivity can result in potential off
target effects. For example, in clinical trials evaluating the safety of engineered
T cells expressing an affinity-enhanced TCR against HLA-A*01–restricted MAGE-A3
in patients with myeloma and melanoma, administration of T cells resulted in cardio-
genic shock and death of the first 2 patients within a few days of T-cell infusion; these
events were not predicted by preclinical studies of the high-affinity TCRs. Gross find-
ings at autopsy revealed severe myocardial damage, and histopathologic analysis
revealed T-cell infiltration. No MAGE-A3 expression was detected in heart autopsy tis-
sues. Translational studies revealed that the recognition of an unrelated peptide
derived from the striated muscle-specific protein titin by engineered TCRs caused car-
diac toxicity, which led to the fatal cardiac complications. Another study with MAGE-
3 resulted in neurologic complications, which were attributed to reactivity to previously
unrecognized expression of MAGE-A12 in the brain. Subsequent studies showed
safety of certain targets and currently a majority of ongoing studies in solid tumors
are targeting well studied CTAs, such as NY-ESO1, LAGE 1A, MAGE-A4, and
MAGE-A10. Studies in sarcoma and melanoma have been promising. In NSCLC,
although experience has been limited so far, no additional safety concerns have been
raised and assessment of safety and clinical efficacy is ongoing in several studies.

Adaptive cellular therapies are holding a great promise for the treatment of solid ma-
lignancies including lung cancer. Identification of the right patient populations and tu-
mor subsets for these therapies, improvements in the duration of time required from
the production to infusion, the optimization of conditioning regimens, genetic manip-
ulations to overcome challenges related with T-cell trafficking, and further
understanding of the tumor and tumor microenvironment are some of the ongoing efforts that provide strong hope for the future.

SUMMARY

Immunotherapy, targeted therapy, and adoptive T-cell therapy have revolutionized cancer research, added to the clinical therapeutic armamentarium, and created novel options for single, combined, or salvage modality therapies in solid organ malignancies. These tremendous advancements are most encouraging for lung cancer, which remains the leading cause of cancer related mortality. As these therapies continue to be studied and refined, it is the authors’ hope that they eventually will safely enter the algorithms of standard therapeutic regimens.

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