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Precision Therapy for Lung Cancer: Tyrosine Kinase Inhibitors and Beyond

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Abstract

For patients with advanced cancers there has been a concerted effort to transition from a generic treatment paradigm to one based on tumor-specific biologic, and patient-specific clinical characteristics. This approach, known as precision therapy has been made possible owing to widespread availability and a reduction in the cost of cutting-edge technologies that are used to study the genomic, proteomic, and metabolic attributes of individual tumors. This review traces the evolution of precision therapy for lung cancer from the identification of molecular subsets of the disease to the development and approval of tyrosine kinase, as well as immune checkpoint inhibitors for lung cancer therapy. Challenges of the precision therapy era including the emergence of acquired resistance, identification of untargetable mutations, and the effect on clinical trial design are discussed. We conclude by highlighting newer applications for the concept of precision therapy.

Keywords

precision medicine; non–small cell lung cancer; ALCHEMIST; MATCH trial; exceptional responders initiative; immune checkpoint inhibitors

INTRODUCTION

With an estimated 224,000 cases diagnosed in 2014, lung cancer continues to account for a large share of the cancer burden in the United States. Additionally, the estimated 159,000 deaths related to this disease account for 27% of all cancer deaths, and the overall 5-year survival for patients with lung cancer remains distressingly low (17%).[1] Non–small cell lung cancer (NSCLC) is the most common type of lung cancer, and adenocarcinoma is the most common histologic subtype of this disease.[2] Unfortunately most of patients with lung cancer are diagnosed with locally advanced or metastatic disease which is unamenable to surgical resection or definite radiation therapy; the 5-year survival of these patients is 4%.[1]

Advanced NSCLC has traditionally been treated with platinum-doublet chemotherapy with the addition of the vascular endothelial growth factor inhibitor, bevacizumab when clinically indicated. Response rates (RRs) of 12%−37% have been observed in the frontline setting

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with median overall survival (OS) ranging from 10–14 months.[3] The identification of molecular subsets of NSCLC in the genomic era, and the development of drugs targeting specific oncogenic mutations have resulted in significant alterations in the management of advanced lung cancer. These changes provide a vivid illustration of the evolution of the therapeutic paradigm from a “one-size-fits-all” approach to that of “precision therapy” with the biology of the disease forming the bedrock of treatment choice. In this article we focus on the identification of molecular subsets of NSCLC and describe the effect of these discoveries on clinical management of advanced NSCLC, as well as its effects on clinical trial design.

CLASSIFICATION OF NSCLC: EFFECT OF THE GENOMIC ERA

The classification of NSCLC has traditionally been based on the histologic appearance of the tumor supplemented by information provided by immunohistochemistry.[4] With the advent of genomic testing, it has been recognized that NSCLC is composed of multiple molecular subsets with distinct phenotypes, natural histories, and sensitivities to targeted therapies. The discovery of oncogenic drivers, which has been facilitated by large multi-institutional studies using cutting-edge genomic technologies forms the bedrock of precision therapy for lung cancer.[5–8]

The Cancer Genome Atlas Project

The Cancer Genome Atlas (TCGA) analysis of lung cancer was conducted to identify molecular alterations in NSCLC and uncover potential targets for biologic therapy. Tumor samples and matched normal controls from patients with previously untreated NSCLC (230 adenocarcinomas and 178 squamous cell carcinomas) were analyzed using multiple platforms including whole genome, messenger RNA, and microRNA sequencing, as well as DNA copy number, methylation, and proteomic analyses.[5,7] These studies confirmed the presence of a large number of somatic mutations in NSCLC (mean mutation rate per megabase, adenocarcinoma:8.9, squamous cell carcinoma: 8.1) including statistically significant mutations in 18 genes in adenocarcinoma and 11 genes in squamous cell carcinomas. Adenocarcinomas without known oncogenic mutations (*EGFR*, *KRAS*, and *BRAF*) were found to harbor aberrations in *NF1*, *RIT1*, *KEAP1*, *TP53*, *MET*, and *ERBB2*. Biologic pathways with recurrent alterations included the RTK/RAS/RAF, PI3K/mTOR, p53, and oxidative stress response pathways, cell cycle regulators, and chromatin and RNA splicing factors. Squamous cell carcinomas nearly always harbored mutations in *TP53*. Other important findings in squamous cell carcinomas included newly discovered loss-of-function mutations in the human leukocyte antigen-A class 1 major histocompatibility gene, and recurrent alterations affecting the PI3K/AKT, CDKN2A/RB1, NFE2L2/KEAP1/CUL3, and SOX2/TP63/NOTCH1 pathways.

Lung Cancer Mutation Consortium Trial

The Lung Cancer Mutation Consortium (LCMC) conducted a study designed to determine the frequency of 10 oncogenic drivers in lung adenocarcinoma, select treatment based on the identified target, and determine survival.[8] Unlike the TCGA project, tumors analyzed in the LCMC study were derived from patients with advanced or recurrent adenocarcinoma of the

lung. More than 50% of the patients had received prior chemotherapy, and analyzed tumor specimens were not exclusively obtained by surgical resection. Among 1102 eligible patients, analysis of at least 1 gene was possible in 1007 patients including 341 (34%) never-smokers. Tumor samples were screened for *EGFR*, *KRAS*, *ERBB2*, *AKT1*, *BRAF*, *MEK1*, *NRAS*, and *PIK3CA* mutations, as well as *ALK* rearrangements and *MET* amplification. Full genotyping was feasible in 733 (67%) cancers, and an oncogenic driver was detected in 466 (64%) cases (Fig. 1). Based on these results, 260 (26%) patients received appropriate targeted therapy, and had a median survival of 3.5 years compared with 2.4 years for 318 (32%) patients with an oncogenic driver who did not receive genotype-targeted therapy ($P = 0.006$). This study demonstrated the feasibility of conducting comprehensive molecular profiling in patients with advanced adenocarcinoma of the lung, and suggested that targeted therapy based on molecular profiling improved patient survival.

PRECISION THERAPY BASED ON GENOMIC DATA

The identification of molecular subsets of lung cancer has resulted in the exponential growth of biologic agents designed to target specific oncogenic drivers. Scores of drugs are at various stages of development and a few small molecule tyrosine kinase inhibitors (TKIs) have been approved by the U.S. Food and Drug Administration (FDA) for treatment of NSCLC with EGFR mutations or ALK translocations.[9]

NSCLC With EGFR Mutations

In-frame deletions in exon 19 and the L858R substitution in exon 21 account for 90% of all mutations in the tyrosine kinase domain of the EGFR gene, and confer sensitivity to EGFR TKIs.[10] Several randomized clinical trials have demonstrated the ability of EGFR TKIs to significantly improve RRs and progression-free survival (PFS) in NSCLC harboring EGFR sensitizing mutations (Table 1).[11–17] In May 2013 the U.S. FDA approved the use of the competitive EGFR inhibitor, erlotinib for first-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 substitution mutations based on the results of the randomized, phase III European Tarceva vs Chemotherapy (EURTAC) trial. In this study, 174 patients with previously untreated meta-static NSCLC harboring the aforementioned sensitizing mutations were randomized to receive frontline treatment with platinum-doublet chemotherapy or oral erlotinib at a dose of 150 mg daily. The primary end point of the study was investigator-assessed PFS. The results demonstrated a clear benefit of erlotinib with a median PFS of 9.7 months in the erlotinib arm vs 5.2 months in the chemotherapy arm (hazard ratio [HR] = 0.37; 95% CI: 0.25–0.54; $P < 0.0001$). Erlotinib was well tolerated; treatment-related serious adverse events (AEs) were observed in 6% of patients in the erlotinib arm vs 20% in the chemo-therapy arm.[11]

In July 2013, afatinib, a second-generation, non-competitive TKI targeting all members of the ErbB family of receptors was approved as frontline therapy for patients with NSCLC with EGFR-deletion 19 and L858R mutations. Approval was based on the results of a randomized, phase III trial (LUX-Lung 3) that showed an improvement in PFS with oral afatinib at a dose of 40 mg daily vs up to 6 cycles of cisplatin and pemetrexed in patients with advanced EGFR-mutated NSCLC.[15] Among 345 patients randomized to treatment, the

median PFS was 11.1 months in the afatinib arm and 6.9 months in the chemotherapy arm (HR = 0.58; 95% CI: 0.43–0.78; $P = 0.001$). AEs were manageable with the frequency of treatment-related grade ≥3 AEs comparable in both arms (49% in the afatinib arm and 48% in the chemotherapy arm). Afatinib demonstrated comparable benefit in a randomized, phase III trial in treatment-naïve Asian patients with EGFR-mutated NSCLC (LUX-Lung 6) with a median PFS of 11 months in the afatinib group vs 5.6 months in the chemotherapy group (HR = 0.28; 95% CI: 0.20–0.39; $P < 0.0001$).[16] Although neither trial showed an improvement in OS for the entire study populations, an OS benefit was observed in patients with exon 19 deletions, suggesting innate differences between exon 19 deletions and L858R mutations in pulmonary adenocarcinomas.[18]

Despite these impressive results, a significant challenge associated with the use of small molecule TKIs is acquired resistance.[19,20] Several mechanisms account for this phenomenon, the most common of which is the emergence of a secondary mutation (T790M) in exon 20, which is detected in approximately 50% of cases.[21] Initial attempts to target the T790M mutation with second-generation EGFR TKIs yielded disappointing results.[22,23] However, 2 new third-generation TKIs that target common EGFR mutations including T790M have shown promising results in early-phase trials (Table 1). In a dose finding study of CO-1686, 88 patients were treated including 55 (63%) with the T790M mutation. A partial response was achieved in 23 of 40 (58%) evaluable patients with a T790M mutation.[24] A phase I study evaluated AZD9291 in 199 patients with EGFR-mutated NSCLC who had developed acquired resistance to EGFR TKIs. Among 107 patients with a T790M mutation, the overall RR was 64% vs 22% in 50 patients without a T790M mutation.[25] Additional therapeutic strategies to overcome acquired resistance to EGFR TKIs are currently under evaluation.[26]

NSCLC With ALK Translocations

ALK translocations were identified as a driver event in NSCLC in 2007.[27] ALK rearrangements occur in 3%−7% of NSCLCs, and the fusion product can be targeted by small molecule TKIs. There are 2 drugs approved for treatment of advanced NSCLC with ALK rearrangements, and others are being evaluated in clinical trials (Table 2).[28–33]

In November 2013 the U.S. FDA approved the use of crizotinib for treatment of metastatic NSCLC with ALK rearrangements. This approval was based on the results of a randomized, phase III trial in which 347 patients with locally advanced or metastatic NSCLC with ALK rearrangements who had received 1 prior line of platinum-containing chemotherapy were randomized to receive oral crizotinib at a dose of 250 mg twice daily or chemotherapy (intravenous pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2 once every 3 weeks). The primary end point was PFS. Patients receiving crizotinib had a median PFS of 7.7 vs 3.0 months for patients in the chemotherapy arm (HR = 0.49; 95% CI: 0.37–0.64; $P < 0.001$). Crizotinib was well tolerated, and AEs were usually mild. The incidence of treatment-related grade 3 or 4 AEs and other serious AEs were similar in the crizotinib and chemotherapy arms (33% vs 32% and 12% vs 14%, respectively).[29]

Ceritinib is an adenosine triphosphate-competitive, TKI targeting ALK with 20 times the potency of crizotinib, which has shown preclinical activity against crizotinib-sensitive, as

well as crizotinib-resistant tumors.[34] Ceritinib was evaluated at doses of 50–750 mg once daily in a phase I study in patients with tumors harboring ALK rearrangements.[30] A total of 130 patients were enrolled including 122 with advanced, previously treated NSCLC of whom 83 (68%) had received crizotinib previously. Ceritinib doses of 400 mg or more per day were administered in 114 patients with NSCLC, and resulted in an overall RR of 58% (95% CI: 48%−67%) and median PFS of 7 months (95% CI: 5.6–9.5 months). Among 80 patients with NSCLC previously treated with crizotinib and receiving at least 400 mg/d of ceritinib, the RR was 56% (95% CI: 45%−67%) and median PFS was 6.9 months (95% CI: 5.3–8.8 months). In April 2014, ceritinib received FDA approval for treatment of patients with metastatic NSCLC with disease progression or intolerance to crizotinib.

Similar to EGFR-targeted therapies, a consequence of prolonged treatment with ALK TKIs is the development of acquired resistance. Multiple mechanisms have been implicated in this phenomenon including development of secondary resistance mutations, amplification of the ALK fusion gene, and activation of bypass pathways including the KIT and EGFR signaling cascades.[35,36] As mentioned above, ceritinib is the first drug approved for treatment of crizotinib-resistant NSCLC with ALK rearrangements. Other drugs that are under evaluation for treatment of ALK resistance include alectinib, AP26113, and heat shock protein 90 (Hsp90) inhibitors including AUY922 and ganetespib.[37] In phase I studies, AP26113 and alectinib have shown promising activity with RRs of 75% and 48% in patients with NSCLC who have progressed on crizotinib.[31,32] Development of acquired resistance remains a recurring problem that limits the benefits of these drugs as illustrated by the occurrence of novel ALK mutations in a patient treated with alectinib.[38] Additional approaches need to be explored to circumvent the problem of acquired resistance including the identification of newer compounds for targeted therapy, evaluation of sequential therapy using existing drugs, and development of patient-derived models of acquired resistance to identify drug combinations that can overcome resistance.[39]

Other Targets for Precision Therapy in NSCLC

In addition to EGFR and ALK, efforts such as TCGA and LCMC have identified several genomic aberrations that have the potential to serve as targets for precision therapy in NSCLC. Examples include BRAF and HER2 mutations and ROS1 gene rearrangements.

The LCMC data showed that the prevalence of BRAF mutations in advanced lung adenocarcinoma is approximately 2%, and these mutations occur more often in current or former smokers.[40] The BRAF inhibitor, dabrafenib has demonstrated activity in a phase II study in patients with advanced NSCLC harboring a BRAF V600E mutation after failure of chemotherapy, with an overall RR of 32%, median duration of response of 11.8 months, and an acceptable safety profile.[41] In January 2014 Dabrafenib received “Breakthrough Therapy” designation by the FDA for treatment of patients with metastatic, BRAF V600E mutation-positive NSCLC who had received at least 1 prior line of platinum-containing chemotherapy.

HER2 mutations and amplifications are found in approximately 2%−6% of NSCLCs. Various attempts at targeted therapy for these mutations/amplifications are presently under evaluation.[8,9,42–44]

ROS1 and RET gene rearrangements have each been identified in 1%−2% of patients with NSCLC. These gene rearrangements result in fusion products with constitutive activation of the respective tyrosine kinases which act as oncogenic drivers.[45] Both ROS1 and RET tyrosine kinases have been shown to be targetable with small molecule TKIs. Owing to structural similarities between the ROS1 and ALK tyrosine kinases, crizotinib is a potent inhibitor of the ROS1 kinase. In a retrospective European study of 32 patients with advanced adenocarcinoma of the lung with ROS1 rearrangements who received crizotinib for off-label use, the overall RR was 80% and median PFS was 9.1 months.[46] These results validate the observations from an expansion cohort of a phase I study of crizotinib in which 50 patients with advanced NSCLC with ROS1 rearrangements were treated with the standard crizotinib dose of 250 mg orally twice daily resulting in a RR of 72% (95% CI: 58%−84%) and median PFS of 19.2 months (95% CI: 14.4 months to not reached).[47] Early reports also document the activity of the RET inhibitors, cabozantinib and vandetanib in patients with NSCLC harboring RET rearrangements.[48,49] Several clinical trials are evaluating other TKIs in patients with ROS1- and RET-positive NSCLC.[9,45]

NEWER CHALLENGES IN THE PRECISION THERAPY ERA

The ability to perform genomic analyses of lung cancers and make treatment decisions based on the identification of oncogenic drivers has resulted in remarkable benefits for patients with advanced disease in need of effective options for systemic therapy. However, these developments have brought into focus a unique set of challenges uncovered by the precision medicine approach.

Undruggable Targets

Although several drugs are being developed to inhibit a variety of oncogenic drivers, some of the most common genetic changes associated with lung cancer have proven to be notoriously difficult to target, and are essentially “undruggable” at present. Of particular relevance in this regard are mutations in RAS and p53. KRAS mutations occur in 20%−30% of NSCLCs.[8] The oncogenic properties of RAS are influenced by high-affinity binding to guanosine triphosphate leading to activation, attachment to the inner aspect of the cell membrane by the process of prenylation, and subsequent activation of downstream signaling pathways including BRAF and PIK3CA, which themselves are also mutated in NSCLC.[50] Farnesyltransferase inhibitors which block prenylation, as well as inhibitors of downstream effectors, such as MEK and PI3K/AKT/mTOR, have been evaluated without much success.[51,52] Nevertheless, renewed efforts to target RAS are focusing on direct RAS inhibitors, novel downstream targets like TBK1, CDK4, and GATA-2, newer methods to target RAS localization, and identification of targets that have synthetic lethal interactions with RAS.[50,53]

Mutations in the tumor suppressor p53 are seen in 46% of lung adenocarcinomas.[7] Although restoring p53 activity has proved to be challenging thus far, there have been renewed efforts in this direction in recent years.[54]

Tumor Heterogeneity

The success of precision medicine is predicated on the accurate identification of genomic aberrations in a tumor. The existence of pretreatment tumor heterogeneity, and clonal evolution following initiation of treatment influence the clinical outcome of precision therapy. Clonal heterogeneity provides an explanation for de novo resistance to a targeted drug, as well as the development of acquired resistance. Efforts are underway to study tumor heterogeneity to better understand the genomic landscape of a tumor both at a certain point in time, as well as longitudinally by acquiring tumor tissue at the time of disease progression. TRAcking non–small cell lung Cancer Evolution through therapy (Rx) (TRACERx) is a prospective trial designed to study intratumor heterogeneity by using an array of techniques including next-generation sequencing, immunohistochemistry, fluorescence in situ hybridization, fluorescence-activated cell sorting, and analysis of circulating tumor cells, as well as circulating tumor DNA. The aims of this trial are to follow tumors from diagnosis to relapse, study the effect of therapy on the evolutionary trajectory of lung cancer, and determine the effects of tumor heterogeneity and clonal dominance on clinical outcome.[55]

Development of Resistance

Presently acquired resistance is an inevitable consequence of precision therapy as illustrated above in reference to the use of EGFR and ALK TKIs. With increasing availability of sophisticated genomic techniques and the development of trials such as TRACERx, significant efforts are underway to delineate the mechanisms of resistance to targeted therapy. As development of resistance is a dynamic process, it is imperative to evaluate a tumor in real time for identification of new genomic abnormalities that mediate acquired resistance. This necessitates a new strategy to evaluate tumors with repeat biopsies at the time of disease progression (Fig. 2). A challenging dilemma is how to deal with radiographic progression when a patient is receiving a targeted drug. It is not uncommon to observe progression of lesions in distinct organ sites, whereas the disease remains stable elsewhere. Additionally, abrupt withdrawal of a targeted agent can precipitate a growth flare owing to the presence of clonal populations of tumor cells that remain sensitive to the targeted drug.[56] Studies have shown that under these circumstances, local therapy for sites of progression and continued use of the targeted agent results in additional clinical benefit.[57] Even in the setting of widespread slow growing disease that meets Response Evaluation Criteria In Solid Tumors (RECIST) guidelines for progression, continuation of the targeted drug can provide sufficient disease control for a considerable period of time.[58]

IMMUNOTHERAPY

Despite the use of cutting-edge technology, a driver event cannot be identified in approximately one-third of patients with NSCLC. In addition, aforementioned issues such as the presence of undruggable targets and the emergence of acquired resistance limits the efficacy of precision therapy for NSCLC based on TKIs alone. The use of immuno-therapy to surmount these challenges has gained widespread recognition in recent years. Several immunotherapeutic interventions have been evaluated with mixed results. Vaccines designed to target proteins such as mucin-1 (MUC-1) and melanoma-associated antigen E-3

(MAGE-3), allogenic whole-tumor vaccines like belagenpumatucel-L and the immunostimulatory compound, talactoferrin alpha failed to demonstrate an improvement in survival in most clinical trials.[59]

Cellular immune responses to normal self-antigens, microbial agents, and cancer cells are regulated by diverse interactions of stimulatory, as well as inhibitory ligands and receptors on lymphocytes, professional antigen presenting cells, as well as cancer cells.[60–62] CTLA-4 is a receptor on T cells, which interacts with B7.1 and B7.2 stimulatory ligands on antigen presenting cells to dampen response of CD28 engagement with these ligands during T-cell activation. CTLA-4 activation results in down modulation of CD4 T cells and enhanced immunosuppressive function of regulatory T cells. Program death-1 (PD-1) is a receptor, which is typically expressed on activated T cells. Engagement of PD-1 with its ligand (PD-L1) on normal cells inhibits destruction of normal tissues during inflammatory responses to infectious agents. Approximately, 50% of lung cancers express PD-1 or PD-L1.[63] Engagement of PD-1 with PD-L1 on cancer cells results in T-cell exhaustion and anergy.

Although the monoclonal antibodies, ipilimumab, and tremelimumab, which inhibit CTLA-4 activation, have been shown to be effective against melanoma, these agents by themselves have limited activity against lung cancer.[61,62] A randomized phase II trial has been performed to evaluate carboplatin and paclitaxel with placebo or ipilimumab (concurrent or phased) in 204 chemotherapy-naïve patients with stage III/IV NSCLC. Steroids (to limit ipilimumab-mediated autoimmune responses) were administered in all arms.[64] The primary end point of the study was immune-related PFS (ir-PFS). Although ir-PFS was improved in the phased treatment vs placebo group (5.7 vs 4.6 months; HR = 0.72; $P = 0.05$), there was no improvement in OS. In an unplanned analysis, PFS and OS appeared to be improved in squamous cell carcinomas.

Carboplatin and paclitaxel with placebo or ipilimumab (concurrent or phased) has also been evaluated in 130 chemotherapy-naïve patients with extensive disease–small cell lung cancer (SCLC) in a randomized phase II trial.[65] Steroids were administered in all arms. The primary end points were ir-PFS and clinical PFS. Although ir-PFS was improved in the phased vs placebo group (6.4 vs 5.3 months, HR = 0.64; $P = 0.03$), there was no improvement in clinical PFS or OS. These studies prompted 2 large randomized phase III trials (NCT01285609 and NCT01450761) evaluating ipilimumab vs placebo with paclitaxel and carboplatin in squamous cell lung cancers, and ipilimumab vs placebo with etoposide and platinum therapy in extensive disease–SCLC, respectively.

A phase I trial has evaluated the safety and clinical activity of an anti-PD-1 antibody (nivolumab) in cancer patients.[66] Clinical responses were observed in 14 of 76 (18%) patients with NSCLC. In another phase I trial, an anti-PD-L1 antibody (BMS-936559) was evaluated in patients with advanced cancers, and objective responses were observed in 5 of 49 (10%) patients with NSCLC.[67] Treatment-related toxicities included fatigue, rash, transaminitis, and pneumonitis (only in the PD-1 trial). Responses in both studies were durable. Subsequent efforts have con-firmed results of these seminal studies.[61,62] RRs in patients with NSCLC treated with nivolumab or pembrolizumab (another humanized monoclonal anti-PD-1 antibody) are approximately 18% with median durations of response

of 74 and 31 weeks, respectively. Rare and fatal pneumonitis has been associated with both of these agents. MPDL3280A is a human monoclonal antibody to PD-L1. RRs in patients with lung cancer following treatment with this antibody are in the range of 23%. No pneumonitis has been observed with this antibody. In general RRs for anti-PD-1 and anti-PD-L1 antibodies appear to coincide with levels of intratumoral PD-L1 expression. Additionally RRs for these antibodies appear to be higher in smokers or former smokers compared with never-smokers, possibly owing to the mutational load in tobacco-associated cancers.

Preliminary results from a phase I study evaluating a combination of ipilimumab and nivolumab in 49 patients with chemo-naïve NSCLC revealed a RR of 16%.[68] Responses were seen in squamous cell and nonsquamous cell cancers, as well as PD-L1 positive and PD-L1 negative tumors. Grades 3 and 4 AEs were seen in nearly 50% of patients. Totally 3 patients died from treatment-related toxicities (respiratory failure, pulmonary hemorrhage, and toxic epidermal necrolysis).

The emergence of immune checkpoint inhibitor therapy represents a major paradigm shift in lung cancer therapy. These impressive results have prompted the initiation of numerous trials evaluating immune checkpoint inhibitors alone or in combination with other agents (Table 3).[61,62,69–75]

EFFECT OF THE PRECISION THERAPY ERA ON CLINICAL TRIAL DESIGN

Traditional clinical trial designs with enrollment predicated on histology and end points based on the phase of the clinical trial are not well suited for evaluating targeted therapies in patients with tumors harboring specific genomic abnormalities. Early-phase proof-of-concept studies with novel designs to match a targeted treatment to its corresponding molecular abnormality provides a more efficient means of evaluating precision therapy.[76] These studies can be histology-independent, and based on specific molecular abnormalities (also known as basket trials) or histology-based, and designed to evaluate multiple molecular abnormalities (umbrella trials). An alternative approach is to consider single patient (*n*-of-1) trials in which an individual patient receives precision therapy for a specific molecular abnormality.[77]

The U.S. National Cancer Institute (NCI) has developed a series of precision medicine initiatives that illustrate the use of these novel clinical trial designs. These include the NCI Molecular Analysis for Therapy Choice (MATCH) trial, Adjuvant Lung Cancer Enrichment. Marker Identification and. Sequencing Trials (ALCHEMIST), Lung Cancer Master Protocol (Lung-MAP), and the Exceptional Responders Initiative.[78]

NCI MATCH is an example of a prospective basket trial that will enroll patients with relapsed or refractory, advanced or metastatic solid tumors or lymphomas that harbor actionable mutations.[78] A mandatory pretreatment biopsy will be performed, and a targeted next-generation sequencing assay will be used to analyze approximately 200 genes. Patients with actionable mutations will receive appropriate targeted therapy and be followed for

response and PFS. At progression patients will be eligible for rebiopsy and further targeted therapy if additional mutations are detected.

The ALCHEMIST trial and Lung-MAP are examples of umbrella trials. The ALCHEMIST trial is designed to evaluate the benefit of adding erlotinib or crizotinib to standard adjuvant therapy vs adjuvant therapy alone, in resectable, early-stage lung cancer harboring EGFR mutations or ALK trans-locations respectively.[78] Lung-MAP will enroll patients with advanced squamous cell carcinoma of the lung who have progressed after frontline therapy and evaluate targeted therapies based on the results of an NGS panel of approximately 250 genes.[78,79] Patients with tumors harboring actionable mutations will be assigned to a substudy that uses a phase II/III trial design. A phase II interim analysis will determine if the assigned intervention is beneficial based on a predefined improvement in PFS. Co-primary end points for the phase III component will be assessment of PFS and OS. Selection of drugs for the various substudies that comprise Lung-MAP will be a fluid process that is based on the latest findings from ongoing precision medicine studies. Initially Lung-MAP will consist of 5 substudies with 10 treatment arms. Among these substudies 4 will enroll patients based on the presence of a relevant biomarker and will compare appropriate precision therapy with chemotherapy or a combination of precision therapy and chemotherapy with chemotherapy alone. If the patient's tumor does not harbor a biomarker that can be paired with a study drug, the patients will be assigned to a "nonmatch" arm, and will be randomly assigned to receive immunotherapy vs standard chemotherapy.

The Exceptional Responders pilot study aims to use genome sequencing to understand the molecular basis of an exceptional response of an individual patient to a targeted agent to which most patients do not usually demonstrate significant or durable response. Eligible patients should have demonstrated a complete response or partial response lasting for at least 6 months to a drug whose overall response is less than 10%.[78,80] The exceptional responders initiative illustrates the concept underlying *n*-of-1 studies.

FUTURE AVENUES

Despite several challenges that need to be overcome, precision medicine has yielded impressive dividends for patients with advanced cancers, including NSCLC. In the future, it is conceivable that the benefits of precision medicine will extend beyond the discovery of genomic aberrations and the development of TKIs to target these abnormalities (Fig. 3). Novel targets that are being explored for precision therapy include chemokines and their receptors and aberrant glycosylation associated with cancer.[81,82] Immunotherapy provides a vivid example of the concept of precision medicine. Several clinical trials exploring different immunotherapeutic interventions to treat a variety of tumors have been successfully completed in recent years.[83] A personalized approach to immunotherapy could involve recognition of tumor heterogeneity, identification of tumor-specific antigens, detection of differences in antitumor immunity in individual patients, and development of adoptive T-cell therapies.[84] Precision therapies could potentially involve RNA interference after identification of microRNA-based signatures of individual tumors.[85] Finally, the possibility of coupling information about tumors gained from various molecular methods with nanomedicine to improve diagnostic tools and drug delivery is under evaluation.[86]

Integration of these approaches to generate robust therapies to target individual tumors could be considered the holy grail of precision medicine.

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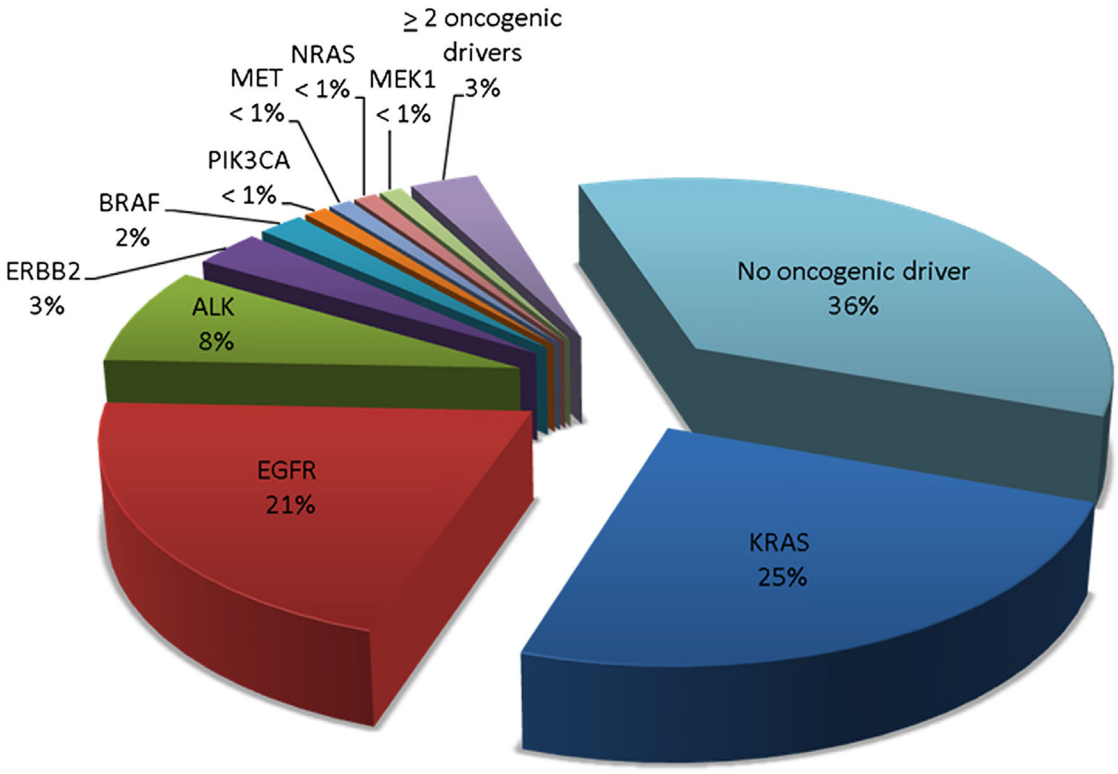

Figure 1.

Frequency of oncogenic drivers in adenocarcinoma of the lung detected by the Lung Cancer Mutation Consortium.[8]

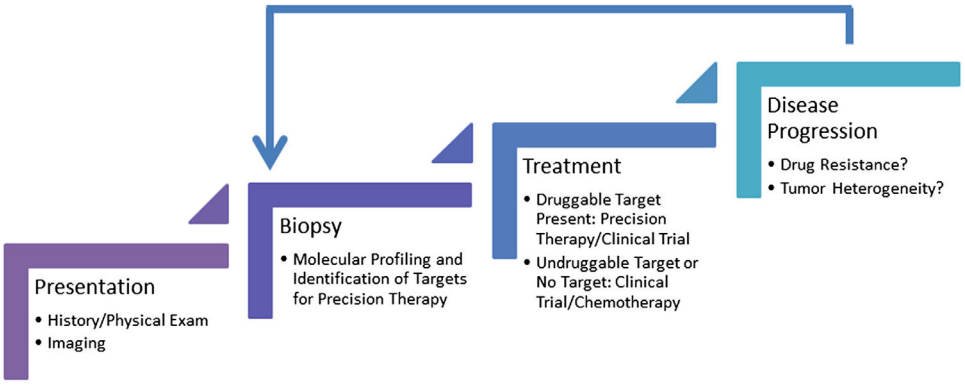

Figure 2.

The precision therapy paradigm. Successful application of the concept of precision medicine relies on the ability to identify constantly evolving molecular aberrations that occur in response to treatment and as a result of the passage of time. The initial step in this process is to obtain sufficient tissue at the time of diagnosis for molecular profiling and identification of targets for precision therapy. The initial choice of systemic therapy should be based on the presence of a druggable target. Upon disease progression, attempts should be made to acquire tumor tissue from the sites of progression to perform molecular analyses and determine the cause of treatment failure.

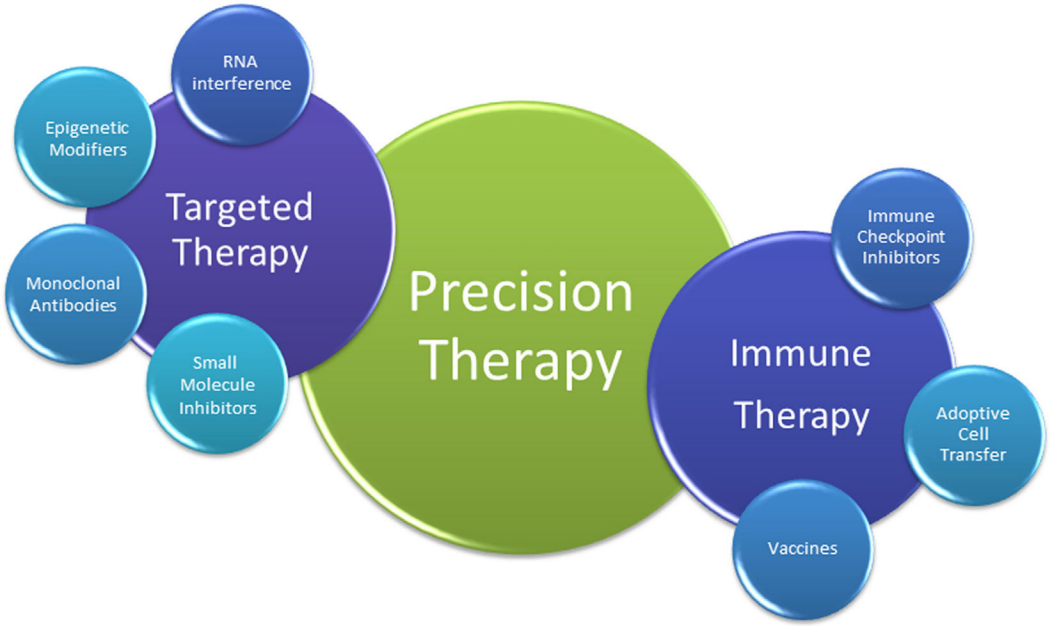

Figure 3.

The components of precision therapy. Abnormalities in the genome, epigenome, and transcriptome can be targeted using several interventions including small molecule inhibitors, monoclonal antibodies, epigenetic strategies, and small interfering RNAs. Immune dysregulation can be targeted using vaccines against tumor-specific antigens, immune checkpoint inhibitors to block cell surface inhibitory molecules, and adoptive cell transfer technologies.

Table 1.

Selected Trials of EGFR Tyrosine Kinase Inhibitors in Patients With EGFR Activating and Acquired Resistance Mutations

Trial[Ref] (Clinical Trial ID)	Phase	Drug	Line of Treatment	Tumor Mutation Status	Patients Enrolled	Response Rate (%)	Median PFS (mo)	Hazard Ratio for PFS
EURTAC[11] (NCT00446225)	III	Erlotinib Platinum-doublet *	Front line	EGFR del 19 or L858R	174	58 15	9.7 5.2	0.37
OPTIMAL[12] (NCT00874419)	III	Erlotinib Carboplatin + gemcitabine	Front line	EGFR del 19 or L858R	154	83 36	13.1 4.6	0.16
NEJSG 002[13] (UMIN000000376)	III	Gefitinib Carboplatin + paclitaxel	Front line	EGFR del 19, L85SR, L861Q, G719A, G719C, G719S	200	74 31	10.8 5.4	0.30
WJTOG3405[14] (UMIN000000539)	III	Gefitinib Cisplatin + docetaxel	Front line	EGFR del 19 or L858R	177	 62 32	9.2 6.3	0.49
LUX-Lung 3[15] (NCT00949650)	III	Afatinib Cisplatin + pemetrexed	Front line	EGFR del 19, L858R or other activating mutations	345	56 23	11.1 6.9	0.58
LUX-Lung 6[16] (NCT01121393)	III	Afatinib Cisplatin + gemcitabine	Front line	EGFR del 19, ins 20, L858R, L861Q, G719A, G719C G719S, T790M, S7G8I	364	67 23	11.0 5.6	0.28
NCT00818441 †,[17]	II	Dacomitinib	Front line	EGFR del 19, L858R	45	76	18.2	
TiGERX ‡,[24] (NCT01526928)	I	CO-1686	Relapse after prior EGFR TKI therapy	T790M present	40	58	Not reached	
AURA[25] (NCT01802632)	I	AZD9291	Relapse after prior EGFR TKI therapy	T790M present T790M absent	107 50	64 22	Not reported Not reported	

del, deletion; ins, insertion; Ref, reference.

* Cisplatin + docetaxel or gemcitabine, or carboplatin + docetaxel or gemcitabine.

† Results from EGFR del 19 or L858R-positive patients only.

‡ Results from T790M+ patients within the therapeutic dose range.

Table 2.

Selected Trials of ALK Inhibitors in Advanced NSCLC Harboring ALK Rearrangements

Trial[Ref] (Clinical Trial ID]	Phase	Drug	Line of Treatment	Patients Enrolled	Response Rate (%)	Median PFS (mo)	Hazard Ratio for PFS
PROFILE 1014[28] (NCT01154140)	III	Crizotinib Pemetrexed + Platinum [*]	Front line	172 171	74 45	10.9 7.0	0.45
PROFILE 1007[29] (NCT00932893)	III	Crizotinib Pemetrexed or Docetaxel	Second line	173 174	65 20	7.7 3.0	0.49
NCT01283516[†,30]	I	Ceritinib	Relapse after prior chemotherapy or crizotinib	114	58	7.0	
NCT01449461[‡,31]	I/II	AP26113	Relapse after prior crizotinib	16	75	Not reported	
NCT01588028[32]	I	Alectinib	Relapse after prior chemotherapy and crizotinib	37	48	Not reached	
JapicCTI 101264[§,33]	I/II	Alectinib	Relapse after prior chemotherapy but ALK inhibitor-naive	46	94	Not reported	

Ref, reference.

[*] Cisplatin or Carboplatin.

[†] Data for patients with NSCLC treated with ceritinib doses ≥400 mg/d.

[‡] Data from ALK-positive NSCLC patients previously treated with crizotinib.

[§] Data from the phase II portion of the study.

Table 3.

Selected Trials of Immune Checkpoint Inhibitors in Patients With Advanced NSCLC

Drug[Ref]	Target	Patient Characteristics		Patients Enrolled	Response Rate (%)	Progression-Free Survival (wk)	Overall Survival (wk)	Clinical Trial ID
		Line of Treatment	Histology					
Nivolumab[69]	PD-1	Front line	Sq Non-Sq	9 11	22 36	15 47	68 NR	NCT01454102
Nivolumab + Chemo[70] N 10 mg/kg + Gem/Cis N 10 mg/kg + Pem/Cis N 10 mg/kg + Pac/Car N 5 mg/kg + Pac/Car	PD-1	Front line	Sq Non-Sq Sq + non-Sq Sq + non-Sq	12 15 15 14	33 47 47 50	25 30 21 31	51 83 65 NR	NCT01454102
Nivolumab + Ipilimumab[68] N 1 mg/kg + Ipi 3 mg/kg N 1 mg/kg + Ipi 3 mg/kg N 3 mg/kg + Ipi 1 mg/kg N 3 mg/kg + Ipi 1 mg/kg	PD-1, CTLA-4	Front line	Sq Non-Sq Sq Non-Sq	9 15 9 16	11 13 33 13	9 33 21 10	44 NR NR NR	NCT01454102
Nivolumab + Erlotinib[71]	PD-1, EGFR	Chemo-naïve; EGFR TKI-naïve, post-EGFR-TKI	Non-Sq	21	19	29	NR	NCT01454102
Nivolumab[72]	PD-1	Relapsed	Sq + non-Sq	129	17	10	43	NCT00730639
Pembrolizumab[73,74]	PD-1	Front line Relapsed	Sq + non-Sq	45 217	26*,† 20	27* 11*	Not reported Not reported	NCT01295827
MEDI4736[75]	PD-L1	Front line + relapsed	Sq + non-Sq	155	16†	Not reported	Not reported	NCT01693562

Carbo, carboplatin; Cis, cisplatin; EGFR, epidermal growth factor receptor; Gem, gemcitabine; Ipi, ipilimumab; N, nivolumab; Non-Sq, nonsquamous; NR, not reached; Pac, paclitaxel; Pem, pemetrexed; Ref, reference; Sq, squamous; TKI, tyrosine kinase inhibitor.

*Central review using RECIST version 1.1.

†In response-evaluable patients.