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Clinician Perspectives on Current Issues in Lung Cancer Drug Development

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Abstract

Recent advances in molecularly targeted therapy and immunotherapy offer a glimmer of hope for potentially realizing the dream of personalized therapy for lung cancer. This article highlights current questions in clinical trial design, enrollment strategies and patient focused drug development, with particular emphasis on unique issues in trials of targeted therapy and immunotherapy.

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INTRODUCTION

Lung cancer continues to be the leading cause of cancer-related mortality in the United States.[1] Recent advances in molecularly targeted therapy and immunotherapy offer a glimmer of hope for potentially realizing the dream of personalized therapy for lung cancer. The year 2015 was an unprecedented year for non-small cell lung cancer (NSCLC) approvals, with seven FDA approvals, including approvals of four therapies with breakthrough therapy designation, three accelerated approvals, and four expedited reviews (table 1, figure 1).[2] While 2015 was a banner year in terms of NSCLC drug approvals, there are many remaining questions from clinicians, patients, investigators and regulators on how to continue to improve the survival of patients with this devastating disease. These issues were discussed at an educational symposium held by the FDA in July 2015. This article highlights these current questions related to clinical trial design, enrollment strategies and patient focused drug development, with particular emphasis on unique issues in trials of targeted therapy and immunotherapy.

TRIAL DESIGN CONSIDERATIONS

The progress in clinical trials in lung cancer is reflected in the changing definition of what is considered “standard of care”. Docetaxel was the most common control arm in second line clinical trials, but the recent approval of immune checkpoint inhibitors based on survival advantages over docetaxel has likely established new standards of care.[3–5] With this come other challenges to open and enrolling studies. If the standard of care substantially changes mid-trial, some have asserted that it is reasonable to amend protocols to provide the new and improved standard of care as the control arm. A case in point is the Lung-MAP second line trial for squamous lung cancer, where changes to the docetaxel control arm were implemented. While regulatory approval does not require a comparative efficacy standard (i.e. improvement over best available therapy) as a trigger for a change in the control arm, a new standard of care changes the calculation that patients and physicians make when deciding to enroll in clinical trials and may dramatically change rates of accrual. Use of more efficacious standard of care in the control arm may result in a smaller expected effect size for the experimental regimen, which may lead to increases in sample size. Development of modeling approaches to simulate the expected performance of a control arm could be helpful to inform trial designs.

While RCTs confirmed the superiority of EGFR and ALK therapy in EGFR mutant and ALK rearranged NSCLC over chemotherapy, such randomized studies may not be feasible for studies of targeted therapeutics in patients whose tumors are driven by even rarer molecular variants (e.g. with a frequency of 1% or less). In addition, for agents with high ORR and duration of response (DoR) in early clinical development, there may not be equipoise to conduct a study against a marginally effective chemotherapy control.[6] In these settings, non-randomized, historically-controlled trials may be necessary to establish clinical benefit.[7] For biomarker-enriched subsets, it will be important to collect the natural history of the disease to better understand the prognostic features of the given subset. Companion diagnostics developed using broader next generation sequencing based platforms or plasma cfDNA may also be necessary for future clinical trials, given tissue scarcity in metastatic

NSCLC and the potential morbidity of repeated biopsy. These multiplexed platforms will also assist in identification of rare molecular subsets for enrollment into clinical trials.

Survival is surprisingly long for some patients treated with targeted therapies or immunotherapies. The importance of the "tail" of the survival curve for patients and physicians has been highlighted in a recent commentary.[8] It is important to conduct well-designed correlative studies on specimens from these long-term responders and survivors with the goal of identifying markers of long-term response.

Clinical trials of adjuvant therapy for lung cancer have historically relied on OS as the benchmark of success. Many of these patients have recurrence, or a second primary, some of whom can still be managed with curative intent if no distant metastases are seen. In addition, post-progression therapies can confound the effect of the adjuvant therapy studied on OS. In view of these issues, disease free survival may be appropriate for use as a surrogate endpoint for survival or as a direct measure of clinical benefit depending on the magnitude of the effect in trials of adjuvant therapy in NSCLC, although some investigators maintain that OS is the endpoint of choice in the adjuvant setting.

Trial design considerations for targeted therapies

Since the initial approval of the first-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) in 2003–2004 for the treatment of metastatic non-small cell lung cancer, several TKIs have been approved. Erlotinib, gefitinib, and afatinib are approved for use in the front-line setting in patients with EGFR exon 19 deletion or exon 21 L858R substitution mutations, with median progression-free survival (PFS) ranging from 10.4 to 11.1 months.[9–13] Osimertinib recently received accelerated approval for use in patients with EGFR T790M mutant tumors who progress on an EGFR TKI.[14] Similar advances in the treatment of ALK rearranged NSCLC have led to the approval of crizotinib in ALK positive metastatic NSCLC, with ceritinib and alectinib receiving accelerated approval for patients with ALK-positive metastatic NSCLC who progressed on crizotinib (table 2). Several targeted therapies, including ceritinib, alectinib and osimertinib received breakthrough therapy designation and subsequently were granted accelerated approved based on durable objective response rate (ORR) in single arm trials, with confirmatory randomized controlled trials (RCTs) ongoing at the time of approval.

With the increasing number of targeted drugs available for use, a critical question is the optimal sequencing of these agents. Is it better to start off with a first generation inhibitor such as erlotinib for EGFR-mutant NSCLC, and reserve the next generation agents for use at the time of disease progression? Or is it better to start with the "next generation agent", hoping to prevent resistance or subclonal selection? Studies such as FLAURA (NCT02296125) and ALTA1-L (NCT02737501) will help to clarify this for EGFR-mutant and ALK positive NSCLC respectively. A potential issue with this approach is that after progression on the next generation TKI, there may be no active targeted agents for a patient to consider. However, there may be situations where patients can be rechallenged with first generations TKIs, as illustrated by a recent report of resensitization to crizotinib mediated by the ALK resistance mutation L1198F, which emerged following progression on an

experimental ALK TKI.[15] Though this mutation confers resistance to the experimental ALK TKI through steric interference with drug binding, it actually enhances binding to crizotinib..

One issue that some clinicians have raised is the use of progression-free survival (PFS) as an endpoint in targeted therapy trials given heterogeneous patterns of disease progression. In the case of slowly progressing disease, solitary lesions (also known as oligo-metastatic lesions) may be effectively controlled with local therapy, such as surgery or stereotactic radiation therapy, with continuation of the TKI for systemic control.[16,17] For these reasons, the community has raised concerns that PFS may not be the optimal endpoint to fully capture benefit in clinical trials of targeted therapies, and that time to switch treatment or time to chemotherapy may be a better means of capturing clinical benefit. A limitation of time to change in treatment is that it is likely to be even less objective than assessment of PFS due to ascertainment bias.

Progression-free survival may be more reflective of benefit when treatment also results in an improvement in or delay in time to onset of lung-cancer specific symptoms based on well validated Patient Reported Outcome (PRO) instruments. Time remaining on therapy following local ablative therapy has been suggested as a means to provide additional information about the benefits of targeted therapies with limited disease progression in one or a small number of lesions. This was evaluated in the ASPIRATION trial, a single arm study where patients who had progressive disease by RECIST (PFS1) on first line erlotinib were allowed to continue on study if per the investigator the patient was continuing to derive benefit. In this study, PFS2 was defined as the time to being taken off erlotinib due to progressive disease, if it was continued beyond RECIST progression. The median time to PFS1 was 11.0 months, and the median time to PFS2 was an additional 3.7 months.[18] The benefits of such a treatment strategy on overall survival (OS) ideally would need to be studied in RCTs.

The optimal management of brain metastases in patients who are candidates for targeted therapy is another area to be considered in the design of clinical trials for targeted therapy drug development. The intracranial penetration of targeted agents varies and may be dose dependent. For patients with EGFR mutant NSCLC with diffuse central nervous system (CNS) progression but controlled extracranial disease on targeted therapy, trial designs allowing whole brain radiation while continuing the current dose of the targeted therapy may be appropriate. Alternative dosing schedules have been investigated. For example, high dose pulsatile weekly EGFR TKI, with or without chemotherapy has been reported to have activity in treating CNS disease.[19] For patients with a few brain lesions amenable to radiosurgery or resection, continuation of TKI following local ablative therapy can also potentially extend disease control.[16] Finally, switching therapy to an agent with better intracranial penetration can be considered. For instance, alectinib has a CNS response rate of 61%, with median response duration of 9.1 months, and can be an option for patients with CNS progression on crizotinib.[20] As successive effective systemic therapies are developed, patients are living longer, and therefore the likelihood of progression in the CNS is increased. The development of targeted therapies that also can penetrate the CNS should continue to remain a priority in future drug development.

Re-biopsies are becoming more common in the management of NSCLC and have been used to guide therapy at progression. It was through re-biopsies that the community learned that EGFR-mutant NSCLC can transdifferentiate into small cell lung cancer, which is treated very differently.[21,22] In addition, re-biopsy facilitated the study of mechanisms of resistance. For example, T790M mutations are detected in about half of patients with EGFR mutations progressing on first-generation EGFR TKIs. A re-biopsy is now necessary to determine whether a patient's drug resistant tumor contains an EGFR T790M mutation in order to be a candidate for osimertinib. In addition, re-biopsy has led to identification of bypass track activation of PIK3CA, MET, BRAF, and HER2 pathways.[23] Emerging questions include how best to combine targeted therapies to address bypass track-mediated resistance. Another question is whether there is a role for PD-1 or PD-L1 inhibitors in *EGFR* mutant and ALK positive NSCLC, given the low mutational burden of these subtypes, and the subgroup analysis from immunotherapy trials suggesting that these patients may derive less benefit from checkpoint blockade.[4] However, the number of patients in these subgroup analyses are small, which limits the power of this analysis, and more data are needed. With the plethora of immunotherapeutic agents in development, the optimal sequencing of targeted agents with immunotherapy also needs to be defined. Ongoing clinical trials seek to address this.

In situations where re-biopsy is not feasible, plasma circulating free tumor DNA (cfDNA) testing offers an alternative approach to detect resistance mechanisms.[24] Detection of cfDNA may more fully capture tumor genomic heterogeneity not possible by analyzing a single drug resistant tumor specimen.[25] Several ongoing trials embed cfDNA to investigate correlative endpoints, and several diagnostic developers are conducting comparisons between cfDNA and tumor tissues in order to analytically validate these assays.[26] If radiographic progression is not observed, or disease progression is indolent, an emerging question is whether detection of a change in biomarker levels in the blood is sufficient to warrant a change in treatment. More large scale studies are needed to establish predictive claims for cfDNA in informing clinical decision-making.

Trial design considerations for immunotherapy

Despite disappointing results in early immunotherapy trials in oncology, many immunologists and clinical investigators were not discouraged. Their efforts provided greater understanding of cancer related immune processes, as summarized in a number of recent reviews.[27,28] One of the steps identified in immune response involves the interaction of cell surface proteins which serve as immune checkpoints. Last year, the results observed with monoclonal antibodies that block the binding of PD-1 ligands to PD-L1 (an immune checkpoint protein) was reported in two RCTs comparing nivolumab to docetaxel in previously treated patients with squamous NSCLC (Checkmate 017) and non-squamous NSCLC (Checkmate 057). These trials led to approval of nivolumab for both indications, based on improvement in OS.[3,4] While the expression of the PD-1 ligand (PD-L1) was neither prognostic nor predictive of benefit in patients with squamous lung cancer, PD-L1 expression appeared to predict for improved OS with all PD-L1 immunohistochemistry (IHC) levels tested (1%, 5% and 10% of tumor cells expressing PD-L1) in non-squamous NSCLC.[3,4] Pembrolizumab, another anti PD-1 monoclonal antibody, was approved under the provisions of accelerated approval for patients with PD-L1 positive (50% or greater

tumor proportion score) NSCLC based on durable response rates in a prospective-retrospective cohort of patients from an expansion cohort of the Keynote 01 study.[29]

Many clinical trials of PD-1 and PD-L1 inhibitors have been pursuing PD-L1 expression as a predictive biomarker and potential companion diagnostic based on an IHC assay. There are two assays for detection of PD-L1 tumor expression that are currently FDA approved.[30] The assays differ in terms of antibody used, assessment method, cut-off values and staining platforms. The comparability of the assays is unknown.

The International Association for the Study of Lung Cancer (IASLC) and other key stakeholders set up a project to analytically compare the various PD-L1 IHC assays. This will be a “comparative study” of four of the PD-L1 assays based on a standardized set of NSCLC tumors. The aim of the study is a comparison of analytical variables as well as the clinically used diagnostic paradigms. The study is ongoing and results from the first part of the study were presented in April 2016 at the AACR annual meeting.

In addition to PD-L1 expression, it appears that the treatment effect with immune checkpoint inhibitors is associated with higher levels of somatic mutations in lung cancers, which results in more neoantigens.[31] In patients with melanoma treated with ipilimumab, longer survival was also observed in patients whose tumors had higher mutational burdens. However, a specific antigenic signature may be more important than the total number of mutations in the T cell response in melanoma patients.[32]

Given the dramatically different mechanism of action of immunotherapies as compared with cytotoxic chemotherapy or targeted therapies, there are questions about the optimal endpoints to study, both to make “go/no-go” decisions and as a surrogate endpoint to predict clinical benefit for regulatory or clinical decision-making. As with melanoma, response by RECIST may not fully capture the clinical benefit of checkpoint inhibitors in patients with NSCLC. The analysis of completed studies for response depth, durability and tumor growth kinetics will be important to investigate whether there is a response index that is useful for “go/no-go” decision making and for characterizing the benefit of these agents. In addition, further characterization of the optimal duration of treatment for patients responding to therapy, and further study of treatment beyond RECIST progression for the minority of patients who may derive continued benefit from this approach is warranted.

In addition to further investigation into response and progression endpoints with immunotherapies, other issues should also be addressed and standardized, including defining dose-limiting toxicity (DLT) criteria, dose escalation rules, assessing reversibility of toxicity, guidelines for re-challenge, and criteria to select dose and schedule of immunotherapies. These considerations are likely to be particularly important in testing the rapidly increasing number of immunotherapy combination regimens.[33] Ongoing and planned trials will evaluate the safety and efficacy of combinations of immune checkpoint inhibitors, immunostimulatory monoclonal antibodies and immune checkpoint inhibitors, cytotoxic and targeted agents plus immunotherapies, monoclonal antibodies and vaccines, and monoclonal antibodies and small molecule immune modulators.[34]

INCREASING ACCRUAL AND STREAMLINING THE CLINICAL TRIAL PROCESS

The current number of adult patients with cancer (less than 5%) who participate in clinical trials is disappointing.[35] With the availability of many promising novel cancer treatments, it is essential to provide effective and safe treatment opportunities as rapidly as possible. The objective of our educational session was to serve as a catalyst for developing ways to enhance clinical trial participation and to streamline clinical trial processes, with the hope that stakeholders will continue to address these critical issues and provide specific recommendations and deliverables.

Several groups have conducted studies which identified potential barriers to participation in clinical trials.[36–38] Despite the strong commitment to performing clinical research, the highest rate of clinical trial participation reported was only 14%. Each group found that lack of an available clinical trial was the most frequent reason for non-participation. Clinical trial accrual has been shown to be inversely related to study development time.[39] It is likely that every clinical investigator has a significant number of patients excluded from clinical trials because of prolonged study activation time. There is no question that study activation is a complex process which requires integration of work done by sponsors, regulators, institutions, and investigators. Increasing communication between these groups would be a good first step to decrease study activation time. This type of collaboration has started with the Clinical Trials Transformation Initiative (CTTI).[40]

Increasing distance from the clinical trial center is another barrier to clinical trial accrual.[36,38] Approximately 15% of patients decline clinical trials because of the distance from the clinical trial center. Time and expense are deterrents to developing clinical trial infrastructure in the community, particularly for small oncology practices. As a direct result of NCI efforts, most patients enrolled in ongoing therapeutic lung cancer studies are enrolled by community-based oncology practices, mainly NCI Community Oncology Research Program (NCORP) sites. In addition, an increasing number of oncologists are employed by hospital-based systems which are providing clinical trial infrastructure.

Trial eligibility criteria need to be re-examined and broadened to provide greater treatment equity and to conduct studies in patient populations which are representative of the general population.[41] Poor performance status is common in lung cancer patients, and these patients are excluded from most studies based on the observation that lethal treatment-related toxicity occurred in 10% of Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2 patients treated with chemotherapy in ECOG lung cancer trials.[42–44] One approach to address this issue would be to reconsider including PS2 patients in studies designed to look at effects in this subgroup separately. For example, a protocol including PS2 patients could pre-specify analyses for safety and efficacy separate from the healthier PS 0 or 1 population. In addition, researchers could consider treating PS2 patients in clinical trials initially at lower doses of cytotoxic agents, with careful dose escalation. It remains to be determined whether similar rates of lethal toxicities will be observed in PS 2 patients treated with immunotherapies and tyrosine kinase inhibitors, given their relatively favorable toxicity profile compared with chemotherapy.

History of a previous cancer is an exclusion criterion in most advanced lung cancer trials. A recent report has shown that 18% of lung cancer patients are excluded from clinical trials because of a previous cancer.[45] In a Surveillance Epidemiology and End Results (SEER) database survey of patients with stage IV lung cancer, a previous cancer had been reported in 15% of patients.[46] Surprisingly, overall survival was superior in the patients who had a previous cancer. This observation suggests that advanced lung cancer patients with a previous diagnosis of cancer should be included in lung cancer trials.

Although the median age for lung cancer patients is 70, the median age in most lung cancer trials is 63 to 64 years.[47,48] The lower rate of treatment of older patients is not limited to clinical trials. In a single institution study, the frequency of systemic therapy in lung cancer patients older than 65 was significantly lower than the rate of treatment in patients less than 65.[49] Based on recent projections, there will be a significant increase in lung cancers in patients over the age of 65 years.[50]

Is risk of increased toxicity a reason to withhold treatment in elderly patients? At least one report suggests that fit elderly lung cancer patients' treatment tolerance is similar to younger patients.[51] With the introduction of targeted therapies and immunotherapies with less toxicity than conventional chemotherapy, advanced age may not be an important limitation. In a small study, elderly lung cancer patients indicated that they want to be involved in the decision making process, and that prolonged survival was their main treatment objective.[52] Changing physician and patient attitudes regarding cancer treatment and age could increase trial accrual.

Drug development and clinical trial development are becoming increasingly complex, labor intensive, and expensive. Simultaneously, the use of electronic medical records and information technologies are expanding rapidly. Considering this, the question to be addressed is whether data which are being entered and submitted on paper or electronic case reports forms be entered directly from electronic medical records into electronic clinical trial databases.

The American Society of Clinical Oncology (ASCO) Targeted Agent and Profiling Utilization Registry (TAPUR) trial will use the Syapse Platform to automate study workflow, including integration of molecular information, monitoring data, and safety reports.[53] In addition, the Syapse platform will be used to capture structured data for clinical history, treatments, and outcomes.

Implementing informatics platforms which can directly import data from electronic medical records into clinical trial databases should reduce repetitious tasks, provide real-time information regarding efficacy and safety, reduce re-entry errors, and reduce clinical trial costs. Although there will be a learning curve with this process, this approach has great promise for streamlining clinical trial processes. In particular, if investigators provide documentation of disease status (response versus stable disease versus progression) at the time of the visits and enter the dates of patient expiration in the electronic medical record when they sign a death certificate, this information which is essential for most clinical trials could be available in real time.

There are other opportunities to increase clinical trial efficiency. One example involves safety reporting for serious and unexpected, suspected adverse reactions (SUSARs) occurring in clinical trials conducted under investigational new drug application (IND). The FDA published a final rule regarding safety reporting in March 2011 and a final guidance regarding this rule in December 2012. It was anticipated that the number of reports would decrease, but the reduction did not occur. Members of the CTTI are addressing how best to communicate how to comply with FDA's statutory requirements for safety reporting to protect the health of patients in the most efficient and effective manner, while reducing the regulatory burdens on investigators and sponsors.[54] With continuing communication between sponsors, regulatory bodies, and investigators, patient safety can be ensured and report quality enhanced, with reduction in unnecessary expedited safety reporting.[55] This outcome should reduce workloads and clinical trial costs. As a starting point, some suggestions for increasing accrual and streamlining clinical trial processes are listed in table 3.

CONCLUSIONS

With the rapid increase in the rate of approvals of drugs and diagnostics for the treatment of NSCLC, including molecularly targeted therapy and immunotherapy, it is important to take a step back and evaluate important clinical issues such as optimal drug sequencing, optimal combinatorial approaches, novel clinical trial designs, and streamlining clinical trial processes. Given the pace of drug and diagnostic development and discovery, it is imperative for all stakeholders to continue communication and interaction to realize the shared objective of converting NSCLC into a chronic disease.

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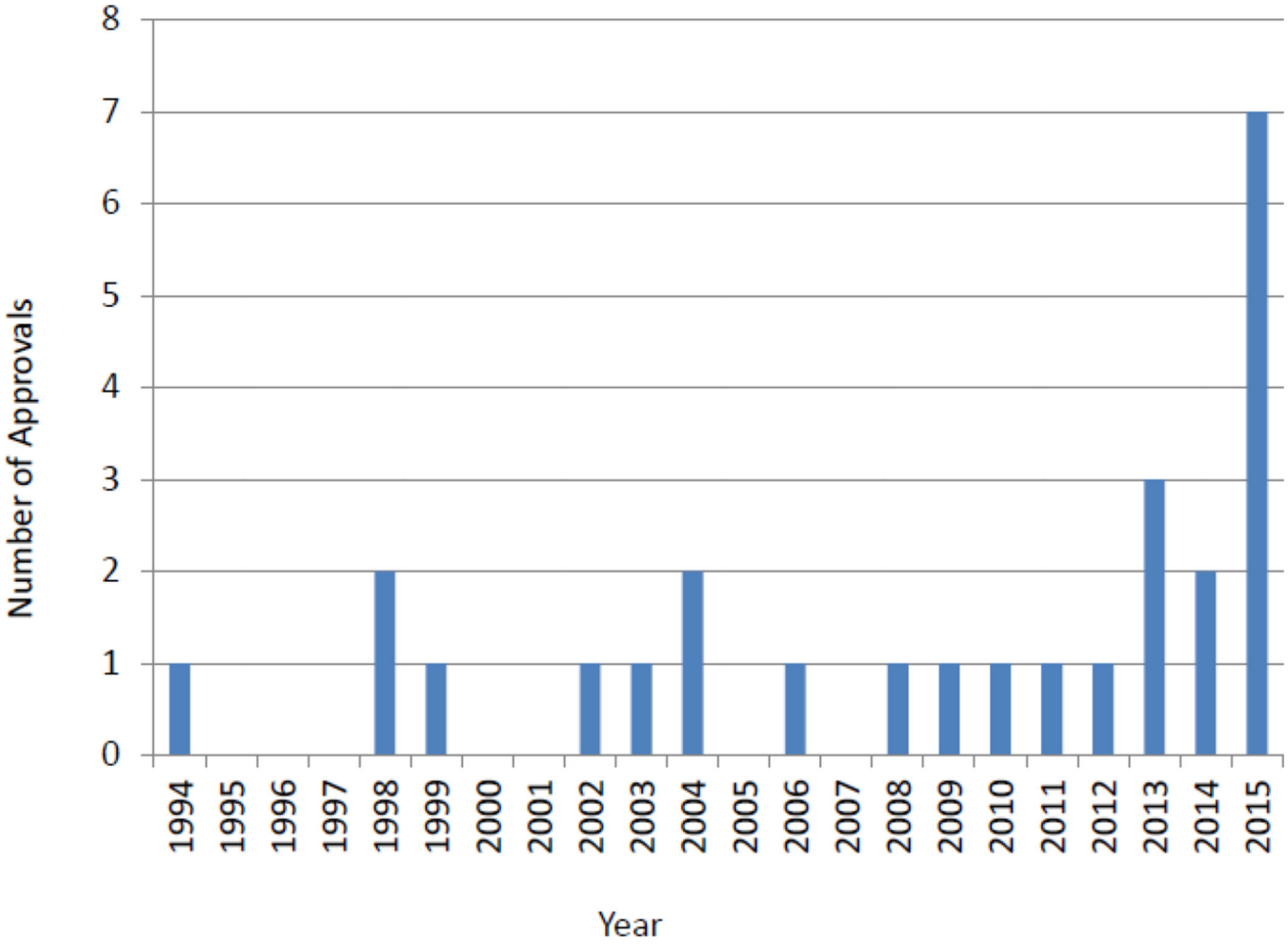

Figure 1.
US FDA NSCLC therapeutic drug approvals by year

Table 1

Therapies that were approved by the FDA for the treatment of NSCLC in 2015

Drug	Mechanism of action	Indication	Companion Diagnostic	Approved dose	Approval Pathways
Nivolumab	Anti-PD1 monoclonal antibody	Metastatic Squamous NSCLC with disease progression following platinum-doublet therapy	None	3 mg/kg IV over 60 minutes every 2 weeks	Expedited Review, Priority Review
Nivolumab	Anti-PD1 monoclonal antibody	Metastatic Non Squamous NSCLC with disease progression following platinum-doublet therapy	Dako PD-L1 IHC 28-8 pharmDx test is complementary, but not required for use of nivolumab	3 mg/kg IV over 60 minutes every 2 weeks	Breakthrough Therapy Designation, Expedited Review, Priority Review
Pembrolizumab	Anti-PD1 monoclonal antibody	PD-L1 positive metastatic NSCLC with disease progression following platinum-doublet therapy	Dako PD-L1 IHC 22C3 PharmDx test	2 mg/kg IV infusion over 30 minutes every 3 weeks	Breakthrough Therapy Designation, Accelerated Approval, Priority Review
Gefitinib	First generation reversible EGFR TKI	Metastatic EGFR mutant (exon 19 deletion or exon 21 L858R) NSCLC	Therascreen EGFR RGQ PCR kit	250 mg orally, once daily, with or without food	
Osimertinib	Third generation irreversible EGFR TKI	Metastatic EGFR T790M mutant NSCLC that have progressed on EGFR TKI	T790M positive by cobas EGFR Mutation Test v2	80 mg orally once daily, with or without food	Breakthrough Therapy Designation, Accelerated Approval, Expedited Review, Priority Review
Alectinib	TKI that targets ALK	ALK positive metastatic NSCLC that have progressed on or are intolerant of crizotinib	None	600 mg orally twice daily with food	Breakthrough Therapy Designation, Accelerated Approval, Expedited Review, Priority Review
Necitumumab in combination with gemcitabine and cisplatin	Recombinant IgG1 monoclonal antibody, binds to human EGFR	First line metastatic squamous NSCLC	None	800 mg IV over 60 minutes on days 1 and 8 of 3 week cycle	

Expedited review = less than 6 month priority review clock

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Table 2

Definitions of FDA expedited development programs

	Fast Track	**Breakthrough Therapy**	**Accelerated Approval**	**Priority Review**
Nature of Program	Designation	Designation	Approval Pathway	Designation
Qualifying criteria	Drug intended to treat serious condition and non clinical or clinical demonstrate potential to address unmet medical need	Drug that is intended to treat serious condition and preliminary evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies	Drug that treats a serious condition and generally provides a meaningful advantage over available therapies and demonstrates an effect on a surrogate endpoint reasonably likely to predict clinical benefit	An application for a drug that treats a serious condition and if approved would provide a significant improvement in safety or effectiveness
Features	Rolling Review	Intensive guidance on efficient drug development; organizational commitment; rolling review	Confirmatory trials to verify and describe the clinical benefit should be ongoing and conducted with due diligence	Shorter clock for review of marketing application (6 months compared with the 10-month standard review)

Table 3

Opportunities to Increase Accrual and Streamline Clinical Trial Processes

Opportunities to Increase Trial Accrual in Advanced Stage lung Cancer Trials	
1	Support CITI efforts to reduce time for clinical trial development and activation
2	Increase number of community based clinical trial centers
3	Relax eligibility criteria
	a. Include patients with a history of previously treated early stage cancer
	b. Include ECOG performance 2 patients and treat at reduced doses of cytotoxic agents
	c. Include ECOG PS 2 patients in trials testing TKIs and immunotherapy
	d. Include patients with treated or untreated brain metastases who are not on glucocorticoids and do not have neurologic symptoms
	e. Reduce time for washout from previous radiation therapy in patients with no radiation toxicity
Strategies to Streamline Clinical Trial Processes	
1	Develop standard electronic case report forms for patients with advanced lung cancer
2	Import data from electronic medical records directly into study data bases
3	Educate pharmaceutical companies, contract research organizations, and academic researchers on regulatory requirements for reporting expedited serious unexpected suspected adverse reactions(SUSARS)
4	Standardize training systems across clinical trials and across pharmaceutical companies
5	Simplify the consent document