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## Non-Small Cell Lung Cancer Clinical Trials Requiring Biopsies with Biomarker-Specific Results for Enrollment Provide Unique Challenges

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### Abstract

**Background**—Clinical trials in lung cancer increasingly require subjects to provide fresh tumor tissue as a prerequisite to enrollment. The effects of this requirement on enrollment rates, enrollment durations, and subject selection have not been fully elucidated.

**Methods**—We retrospectively reviewed data generated by patients who consented to one or more interventional lung cancer clinical trials the UCLA Jonsson Comprehensive Cancer Center between January 2013 and December 2014. Trials were considered to require a biopsy when enrollment was conditional on the procurement of tissue without intervening therapy between procurement and enrollment.

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**Results:** 311 patients underwent 368 screening incidents for one or more of 19 trials. Trials that required a new biopsy had a longer median screening duration (34 vs. 14 days) than trials that did not require a biopsy ( $p < 0.001$ ). Trials requiring a biopsy had a greater screen failure rate (49.1% v. 26.5%,  $p < 0.001$ ), largely driven by patients who did not undergo the required biopsy or lacked the required biomarker. Worsening performance status led to the majority of screen failures (56.5%) among biomarker-eligible patients.

**Conclusions:** Although the scientific benefits of obtaining a new biopsy and requiring specific results for trial enrollment are clear, it leads to a lengthening of the screening period, which, in some cases, is associated with clinical decline prior to enrollment. Implications for the interpretation of data from studies of this design should be explored.

### **Precis for use in the Table of Contents:**

Although the scientific benefits of obtaining a new biopsy and requiring specific results for trial enrollment are clear, studies with such a design lead to a lengthening of the screening period, which, in some cases, is associated with clinical decline prior to enrollment. Implications for the interpretation of data from studies of this design should be explored.

### **Keywords**

oncology; biomarkers; clinical trials; lung cancer; non-small cell lung cancer; immunotherapy; targeted therapy

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## **INTRODUCTION**

Lung cancer leads to more deaths than the next four deadliest malignancies combined.<sup>1</sup> Clinical trials in cancer, including lung cancer, have traditionally identified patients based on histology and clinical characteristics,<sup>2</sup> factors which do not fully account for cancer's heterogeneity.<sup>3</sup> As various oncogenic driver mutations have been discovered and corresponding treatments targeting those mutations developed, survival outcomes for patients have improved.<sup>4</sup> Scientists have been encouraged by these benefits. Pharmaceutical companies have also taken notice, and in the United States, annual spending on molecularly targeted therapies now exceeds spending on conventional chemotherapies.<sup>5</sup>

This movement towards targeted therapies has been particularly embraced in NSCLC, for which patients with metastatic epidermal growth factor receptor (EGFR)-mutant, anaplastic lymphoma kinase (ALK) gene-rearranged cancers, and patients with tumors expressing PD-L1 staining greater than or equal to 50% receive targeted therapies or immunotherapy prior to cytotoxic chemotherapies.<sup>6,7</sup> The Lung Cancer Mutation Consortium showed that the majority of adenocarcinomas of the lung, the most common NSCLC histology, harbored one of several driver mutations, and superior survival was seen when patients were treated with an agent targeting the specific driver mutation in their tumor.<sup>8</sup> Clinical trials and therapies designed to treat specific subgroups promise to provide greater advances in patient outcomes with less time and fewer resources.<sup>2,9</sup> Since 2010, the majority of approval statements issued by the Food and Drug Administration for lung cancer therapies are for subgroups of patients

with specific biomarkers, including EGFR mutations, ALK gene rearrangements, and levels of PD-L1 staining.<sup>10-17</sup>

The importance of identifying biomarkers early in the development cycle is illustrated by the development of gefitinib. After receiving accelerated approval in 2003 for the treatment of all patients with advanced NSCLC after progression on platinum doublet chemotherapy and docetaxel, gefitinib had its approval withdrawn when confirmatory trials failed to show sufficient benefit in a non-biomarker-specific group.<sup>18,19</sup> Only later was it recognized that nearly all responding patients harbored EGFR exon 19 deletions or exon 21 L858R substitution mutations.<sup>6</sup> In 2015, gefitinib was approved again, this time for the treatment of NSCLC patients with these specific mutations.

The American Society of Clinical Oncology recognizes the potential of biomarker-driven research and recently stated that “it is imperative that trial sponsors develop comprehensive biospecimen banks for each trial.”<sup>2</sup> Although archival tissue may be appropriate for the evaluation of predictive biomarkers, it is often insufficient in quantity or quality. Fine-needle aspirations or bronchoscopic biopsies are often insufficient for predictive biomarker validation.<sup>20-23</sup> Even when there is ample tissue, it may not accurately reflect the relevant biology. This can occur based on treatment emergent changes such as EGFR T790M mutations, which occurs after treatment with an EGFR inhibitor. In addition, molecules of interest may deteriorate as time passes.<sup>24</sup>

In January 2013, our program had a tremendous increase in accrual to studies that required subjects to undergo biopsies and wait for tissue to be analyzed prior to enrollment. Therefore, we sought to explore ways in which this design altered the clinical trial process. This included analysis of the following aspects: 1) duration of screening, 2) enrollment vs. screen failure, 3) causes of screen failure, and 4) the ability of enrolled patients to yield meaningful efficacy data by undergoing the first set of protocol-required imaging.

## METHODS

Using UCLA’s electronic database of clinical trial tracking and billing, we identified patients that signed consent for one or more of the 19 lung-cancer focused clinical trials at the UCLA Jonsson Comprehensive Cancer Center between 1/1/2013 and 12/31/2014 (Table 1). Relying on patient charts, electronic health records, and billing records, we identified the date of consent and, as appropriate, date of biopsy, screen failure, treatment, and first radiographic assessment.

A trial was categorized as requiring a biopsy if its inclusion and exclusion criteria called for procurement of fresh tissue and central testing with a specific result as a prerequisite to enrollment. The biopsy requirement was considered waived when there was an availability of recently procured tissue that satisfied screening requirements, which included no intervening therapy between tissue procurement and first treatment on the protocol for which the subject was screening. As some of these trials allowed confirmed biomarker negative patients in specific cohorts, patients who enrolled on biomarker negative cohorts were considered biomarker eligible. Trials without a biomarker requirement and trials in which a

biomarker requirement could be satisfied with archival tissue even when obtained prior to intervening therapy were considered as not requiring a biopsy (Table 2).

Screening duration was defined as the days from consent to either screen failure or intervention (infusion or oral ingestion of study drug). Protocols called for the first radiographic assessment to be done at different time points (range 3 to 9 weeks; median 6 weeks). In order to evaluate the number of enrolled subjects that withdrew prior to first radiographic assessment, we evaluated subjects' withdrawal from study in relation to the first protocol-specific required radiographic assessment.

If a subject consented for the same trial more than once, the earliest date of consent and the latest date of screen failure were recorded, and the entire event was considered to be one screening incident. This tended to occur because of issues that emerged during screening (i.e. brain metastases requiring treatment). Some protocols required these patients to be screen failed and then rescreened. If a subject signed consent and screened for more than one clinical trial, each trial for which the subject screened was considered a unique screening incident.

### Statistical Analysis

Clinical characteristics were compared between patients consenting to trials with biopsy requirements and those without biopsy requirements using the chi-square or Fisher's exact test for categorical variables and t-tests or Wilcoxon tests for continuous variables. Values were summarized using mean (SD) or frequency (percentage) unless otherwise noted. (Table 2)

We then modeled the outcome of screen fail (yes/no) using a generalized estimating equations (GEE) logistic regression model. Variables included in the model were biopsy requirement (yes/no), age, gender, and trial the patient was enrolled in as our clustered effect (to account for potentially correlated patients within each trial). From this model, odds ratios and 95% confidence intervals were extracted for each variable. (Table 3)

Finally, we performed a subgroup analysis on only the patients who did not screen fail to see if patients enrolled in trials requiring biopsies had shorter times until intervention by constructing Kaplan-Meier curves and formally comparing the groups using the log-rank test. (Figure 1)

All analyses were performed using SAS V9.4 (Cary, NC). All tests were two-sided with p-values <0.05 considered statistically significant.

## RESULTS

368 screening incidents occurred on 19 trials over the two-year period (Figure 2). 285 screening incidents occurred for studies in which a biopsy was required. The biopsy requirement was associated with a screen fail rate of 49.1% (140 of 285 incidents) – a rate significantly higher than the 26.5% (22 of 83 incidents) on trials not requiring biopsies (49.1% vs. 26.5%;  $p < 0.001$  using chi-square test). The discrepancy in screen failure rates was not significant when the 56 screening incidents that did not complete biopsies were

excluded from the comparison (36.7% vs. 26.5%;  $p=0.094$ ). In the 229 of 285 (80.4%) screening incidents for which the biopsy requirement was fulfilled, 154 had the biopsy completed and 75 had the biopsy requirement waived due to the availability of adequate archival tissue that met protocol requirements. 50 of the 154 (32.5%) screening incidents with completed biopsies and 34 of the 75 (45.3%) screening incidents with waived biopsies resulted in screen failure.

### Screening Duration

Median duration of screening incidents for subjects with the biopsy requirement waived was 24 days while the median duration of screening incidents for subjects on trials not requiring a biopsy was 15 days (median 24 vs. 15 days;  $p=0.002$ , Wilcoxon). Screening duration was clearly longer on those screening incidents that required a new biopsy (median 35 days) compared either to patients who had the new biopsy requirement waived (35 days vs. 24 days,  $p=0.001$ , Wilcoxon) or to patients who did not require a new biopsy (35 days vs. 15 days,  $p<0.001$ , Wilcoxon). Despite increased experience with this study design over the two-year period evaluated, screening duration did not improve over time (35.2 days in 2013 vs 35.9 days in 2014).

### Causes of Screen Failure

Biomarker positivity on the parent trials was 53–61% with only a small percentage of biomarker negative patients being allowed to enroll in specific cohorts.<sup>9,25</sup> As anticipated, screen failures on trials requiring a biopsy were most commonly due to ineligibility based on the biomarker (61 of 84 patients; 72.6%). However, while worsening performance status was an uncommon cause of screen failures for patients on trials not requiring a biopsy, declining performance status led to the majority of screen failures of biomarker eligible patients on trials requiring a biopsy (56.5% vs. 13.6%;  $p=0.005$ , Fisher's).

### Failure to Stay on Study to First Radiographic Assessment

With the recognition that many screen failures in trials requiring biopsies were due to worsening performance status during screening, we sought to evaluate whether enrolled patients were more likely to withdraw prior to adequately assessing efficacy of the study agent. Subjects who withdrew after enrollment but prior to treatment (1 subject who completed the biopsy requirement and 3 who had it waived) were excluded for this analysis. When comparing trials requiring and not requiring biopsies, there was no difference in the likelihood of failing to stay on study until the first protocol required radiographic assessment (15 of 103 (14.6%) enrolled subjects who completed biopsies, 4 of 38 (10.5%) with waived biopsies, and 4 of 60 (6.7%) on trials not requiring biopsies;  $p=0.306$ , chi-square test).

## DISCUSSION

Our analysis shows that the biopsy requirement with the additional biomarker testing was associated with an increased screening duration and an increased rate of screen failures, driven in part by worsening performance status during screening. Trials requiring tissue as a prerequisite to enrollment are particularly labor intensive,<sup>26</sup> and even more so when that tissue must be from a fresh biopsy. The various divisions and departments in such a

screening process include but are not limited to medical oncology, pathology, and radiology.<sup>27</sup> Although it may be that our site is an outlier with regard to screening duration, we find that unlikely, and other institutions have similarly observed a biopsy requirement to be associated with increased screening times and rates of screen failure.<sup>28</sup> Based on the large number of patients we accrued to studies of this design, we exhaustively evaluated ways to expedite the process. We found that, in addition to the delays related to interdepartmental communication and time taken to evaluate specimens by the study sponsor, mundane issues, such as missing the last parcel delivery service pick up on Thursdays, could lead to a 3-day delay.

Based on nearly half of the patients on the parent trials being biomarker negative, it is surprising that the disparity in the rate of screen failure is not greater. Some biomarker negative patients were enrolled, but the great majority of patients enrolled in cohorts requiring biomarker positivity. Cancer patients are often self-motivated to participate in clinical trials,<sup>29</sup> and although a patient not pursuing a clinical trial would have typically received treatment within one to two weeks at our institution, patients are willing to wait in order to access experimental therapies. These trials were exciting to patients regardless of the additional biopsy requirements, and the rate of withdrawal of consent was quite low. The overall screen failure rate indicates that trials of this design can be conducted in a population that is not “highly selected” when the biomarker is relatively common in the screened population. However, the exclusion of a higher percentage of otherwise eligible patients who were unable to enroll based on worsening performance status demonstrates a potential bias introduced with this study design. Further, 7 biomarker eligible patients withdrew prior to receiving study drug. Some of these are patients who underwent a biopsy and were randomized to control arms of studies from which they then chose to withdraw, another issue deserving of further study.

We found that similar percentages of patients were unable to remain on study long enough to yield optimal radiographic data. It is possible that this indicates little difference in the population of patients enrolled on trials, regardless of a biopsy requirement. However, it is also possible that worsening performance status in patients enrolled was counterbalanced by the inability of the patients with the most tenuous performance status to complete screening.

While there is consensus regarding the value of obtaining tissue from clinical trial participants to the development of the right drugs for the right patients, investigators may wish to find ways to expedite the procurement of tissue, utilizing new biomarker acquisition techniques (i.e., blood assays for biomarker testing), and minimizing the challenges to enrollment that tissue procurement may present. Efficacies of liquid biopsies are improving, but it is unclear that they are ready to replace traditional biopsies.<sup>30-32</sup> Coordination between radiology, pathology and oncology departments is key to ensuring that NSCLC patients on trials requiring a biopsy receive the best opportunity to benefit from clinical trial participation. Further evaluation of trials requiring a new biopsy with specific results required for enrollment and the ways in which studies of this design differ from traditional study designs are warranted.



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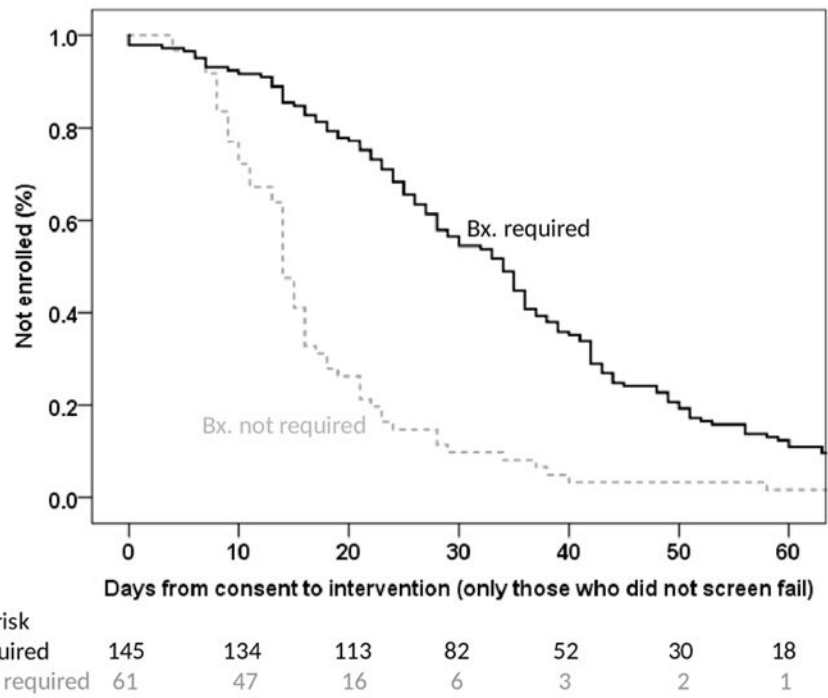
Funding: One Ball Matt Golf Tournament

## References

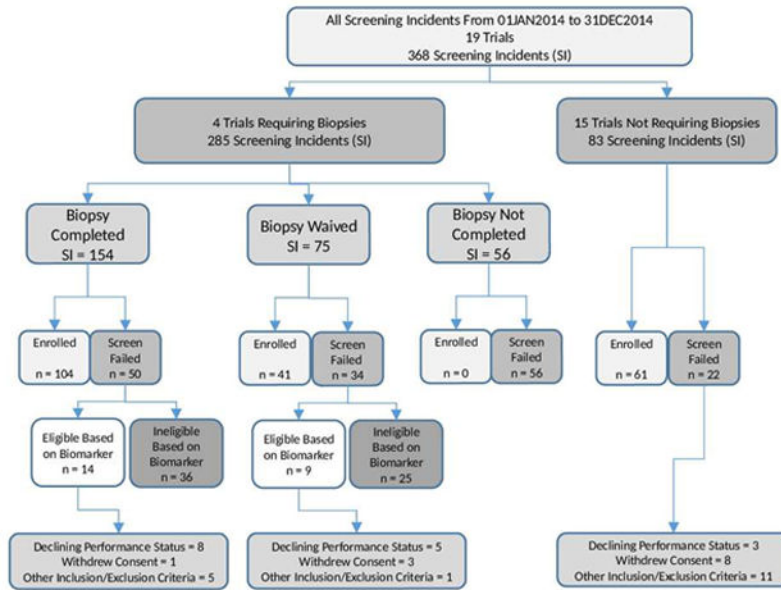
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA: A Cancer Journal for Clinicians*. 2016;66(1):7–30. [PubMed: 26742998]
2. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes. *Journal of Clinical Oncology*. 2014;32(12):1277–1280. [PubMed: 24638016]
3. Sholl LM, Aisner DL, Varella-Garcia M, et al. Multi-institutional Oncogenic Driver Mutation Analysis in Lung Adenocarcinoma: The Lung Cancer Mutation Consortium Experience. *Journal of Thoracic Oncology*. 2015;10(5):768–777. [PubMed: 25738220]
4. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2. *New England Journal of Medicine*. 2001;344(11):783–792. [PubMed: 11248153]
5. Lyman GH, Moses HL. Biomarker Tests for Molecularly Targeted Therapies — The Key to Unlocking Precision Medicine. *New England Journal of Medicine*. 2016;375(1):4–6. [PubMed: 27353537]
6. Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma. *New England Journal of Medicine*. 2009;361(10):947–957. [PubMed: 19692680]
7. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. *New England Journal of Medicine*. 2016;375(19):1823–1833. [PubMed: 27718847]
8. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*. 2014;311(19):1998–2006. [PubMed: 24846037]
9. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. *New England Journal of Medicine*. 2015;372(21):2018–2028. [PubMed: 25891174]
10. Administration FaD. Hematology/Oncology (Cancer) Approvals & Safety Notifications. Available at: <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm>. Accessed September 1, 2015.
11. Zhou C, Wu Y-L, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *The Lancet Oncology*. 2012;13(8):735–742. [PubMed: 21783417]
12. Sequist LV, Yang JC-H, Yamamoto N, et al. Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung Adenocarcinoma With EGFR Mutations. *Journal of Clinical Oncology*. 2013;31(27):3327–3334. [PubMed: 23816960]
13. Douillard JY, Ostoros G, Cobo M, et al. First-line gefitinib in Caucasian EGFR mutation-positive NSCLC patients: a phase-IV, open-label, single-arm study. *Br J Cancer*. 2014;110(1):55–62. [PubMed: 24263064]
14. Yver A. Osimertinib (AZD9291) – a science-driven, collaborative approach to rapid drug design and development. *Annals of Oncology*. 2016.
15. Shaw AT, Kim D-W, Mehra R, et al. Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer. *New England Journal of Medicine*. 2014;370(13):1189–1197. [PubMed: 24670165]
16. Seto T, Kiura K, Nishio M, et al. CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1–2 study. *The Lancet Oncology*. 2013;14(7):590–598. [PubMed: 23639470]
17. Shaw AT, Kim D-W, Nakagawa K, et al. Crizotinib versus Chemotherapy in Advanced ALK-Positive Lung Cancer. *New England Journal of Medicine*. 2013;368(25):2385–2394. [PubMed: 23724913]
18. Fossella F, Pereira JR, Pawel Jv, et al. Randomized, Multinational, Phase III Study of Docetaxel Plus Platinum Combinations Versus Vinorelbine Plus Cisplatin for Advanced Non–Small-Cell



- Lung Cancer: The TAX 326 Study Group. *Journal of Clinical Oncology*. 2003;21(16):3016–3024. [PubMed: 12837811]
19. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *The Lancet*.366(9496): 1527–1537.
  20. Dooms C, Muylle I, Yserbyt J, Ninane V. Endobronchial ultrasound in the management of nonsmall cell lung cancer. *European Respiratory Review*. 2013;22(128):169–177. [PubMed: 23728872]
  21. Du Rand I, Blaikley J, Booton R, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults. *Thorax*. 2013;68(Suppl 1):i1–i44. [PubMed: 23860341]
  22. Knoepp SM, Roh MH. Ancillary techniques on direct-smear aspirate slides. *Cancer cytopathology*. 2013;121(3):120–128. [PubMed: 22786714]
  23. Kothary N, Lock L, Sze DY, Hofmann LV. Computed tomography–guided percutaneous needle biopsy of pulmonary nodules: impact of nodule size on diagnostic accuracy. *Clinical lung cancer*. 2009;10(5):360–363. [PubMed: 19808195]
  24. Jänne PA, Yang JC-H, Kim D-W, et al. AZD9291 in EGFR Inhibitor–Resistant Non–Small-Cell Lung Cancer. *New England Journal of Medicine*. 2015;372(18):1689–1699. [PubMed: 25923549]
  25. Sequist LV, Soria J-C, Goldman JW, et al. Rociletinib in EGFR-mutated non–small-cell lung cancer. *New England Journal of Medicine*. 2015;372(18):1700–1709. [PubMed: 25923550]
  26. Garcia S, Saltarski JM, Yan J, Xie X-J, Gerber DE. Time and Effort Required for Tissue Acquisition and Submission in Lung Cancer Clinical Trials. *Clinical Lung Cancer*. 2017.
  27. Overman MJ, Modak J, Kopetz S, et al. Use of Research Biopsies in Clinical Trials: Are Risks and Benefits Adequately Discussed? *Journal of Clinical Oncology*. 2013;31(1):17–22. [PubMed: 23129736]
  28. Lim C, Sung M, Shepherd FA, et al. Patients with Advanced Non–Small Cell Lung Cancer: Are Research Biopsies a Barrier to Participation in Clinical Trials? *Journal of Thoracic Oncology*. 2016;11(1):79–84. [PubMed: 26762742]
  29. Agrawal M, Grady C, Fairclough DL, Meropol NJ, Maynard K, Emanuel EJ. Patients’ Decision-Making Process Regarding Participation in Phase I Oncology Research. *Journal of Clinical Oncology*. 2006;24(27):4479–4484. [PubMed: 16983117]
  30. Jenkins S, Yang J, Ramalingam S, et al. 134O\_PR: Plasma ctDNA analysis for detection of EGFR T790M mutation in patients (pts) with EGFR mutation-positive advanced non-small cell lung cancer (aNSCLC). *Journal of Thoracic Oncology*.11(4):S153–S154.
  31. Levy B, Hu ZI, Cordova KN, Close S, Lee K, Becker D. Clinical Utility of Liquid Diagnostic Platforms in Non-Small Cell Lung Cancer. *The Oncologist*.2016;21(9):1121–1130. [PubMed: 27388233]
  32. Sorber L, Zwaanepoel K, Deschoolmeester V, et al. Circulating cell-free nucleic acids and platelets as a liquid biopsy in the provision of personalized therapy for lung cancer patients. *Lung Cancer*. 2017;107:100–107. [PubMed: 27180141]



**Figure 1.** Kaplan Meier-plotter comparing enrollment times for subjects screening for trials requiring biopsies and trials not requiring biopsies.



**Figure 2.** Diagram of all screening incidents and subsets used for analysis.

**Table 1a.**

NSCLC trials conducted from 1/1/2013 to 12/31/2014 at UCLA JCCC requiring a biopsy

Trials Requiring a Biopsy		
Clinicaltrial.gov Identifier	Description	Biopsy Qualifier for Trial
NCT01295827 <sup>a</sup>	A Study of MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinomas and Melanoma	PD-L1+
NCT01526928 <sup>a</sup>	A Phase 1/2, Open-Label, Safety, Pharmacokinetic and Preliminary Efficacy Study of Oral CO-1686 in Patients with Previously Treated Mutant EGFR Non-Small Cell Lung Cancer (NSCLC)	T790M+
NCT01905657	A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer	PD-L1+
NCT02147990	A Phase 2, Open-label, Multicenter, Safety and Efficacy Study of Oral CO-1686 as 2nd Line EGFR-directed TKI in Patients with Mutant EGFR Non-Small Cell Lung Cancer (NSCLC) with the T790M Resistance Mutation	T790M+

<sup>a</sup>Patients who were biomarker negative were eligible for select study cohorts within the trials.

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**Table 1b.**

NSCLC trials conducted from 1/1/2013 to 12/31/2014 at UCLA JCCC not requiring a biopsy

<b>Trials Not Requiring a Biopsy</b>	
<b>Clinicaltrial.gov Identifier</b>	<b>Description</b>
NCT01664754	Phase I Dose Escalation Study of Carboplatin, Pemetrexed and Exemestane in Postmenopausal Women with Metastatic Non-Squamous NSCLC
NCT01712217	A Study of HSP90 Inhibitor AT13387 Alone and in Combination with Crizotinib in the Treatment of Non-Small Cell Lung Cancer (NSCLC)
NCT01454102	A Multi-arm Phase I Safety Study of Nivolumab in Combination with Gemcitabine/Cisplatin, Pemetrexed/Cisplatin, Carboplatin/Paclitaxel, Bevacizumab Maintenance, Erlotinib, Ipilimumab or as Monotherapy in Subjects with Stage IIIB/IV Non-Small Cell Lung Cancer (NSCLC)
NCT01237678	A Phase 1/2 Study to Assess the Safety and Efficacy of Lorvotuzumab Mertansine (IMGN901) in Combination with Carboplatin/Etoposide in Patients with Advanced Solid Tumors including Extensive Stage Small Cell Lung Cancer
NCT02079636	A Phase 1b Study of Abemaciclib in Combination with Multiple Single-Agent Options for Patients with Stage IV NSCLC
NCT01900652	A Randomized, Open-Label Phase 2 Study Evaluating LY2875358 Plus Erlotinib and LY2875358 Monotherapy in MET Diagnostic Positive NSCLC Patients with Acquired Resistance to Erlotinib
NCT01577745	A Phase 1, Multicenter, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI0639 as a Single-agent and in Combination Therapy in Adult Subjects with Advanced Solid Tumors, Including Small Cell Lung Cancer
NCT01685060	A Phase II, Multicenter, Single-arm Study of Oral LDK378 in Adult Patients with ALK-activated Non-Small Cell Lung Cancer Previously treated with Chemotherapy and Crizotinib
NCT01465802	A Phase 2 Study of Dacomitinib in Advanced Non-Small Cell Lung Cancer (Post-Chemotherapy or Select First Line Patients) to Evaluate Prophylactic Intervention on Dermatologic and Gastrointestinal Adverse Events and Patient Reported Outcomes
NCT01827267	Phase 2 Study of Neratinib and Neratinib Plus Temezirolimus in Patients with Non-Small Cell Lung Cancer Carrying Known HER2 Activating Mutations
NCT01871805	A Phase I/II Study of the ALK Inhibitor CH5424802/ RO5424802 in Patients with ALK-Rearranged Non-Small Cell Lung Cancer Previously Treated with Crizotinib
NCT00688116	A Phase 1 Study of the HSP90 Inhibitor, Ganetespib, Administered Twice-Weekly in Patients with Solid Tumors
NCT01348126	A Randomized, Phase IIB/III Study of Ganetespib (STA-9090) in Combination with Docetaxel Versus Docetaxel Alone in Subjects with Stage IIIB or IV Non-Small-Cell Lung Cancer
NCT01798485	A Randomized, Phase 3 Study of Ganetespib in Combination with Docetaxel versus Docetaxel Alone in Patients with Advanced Non-Small-Cell Lung Adenocarcinoma
NCT01784640	A Phase IB Dose-Escalation Study of Pemetrexed and AUY922 in Previously-Treated Patients with Metastatic Non-Squamous, Non-Small Cell Lung Cancer

**Table 2.**

Patient Characteristics and Durations of Interest

Patient characteristics	w/o biopsy requirement N = 83	w/ biopsy requirement N = 285	p-value	test	Subset of Patients
Male	29 (34.9%)	129 (45.3%)	0.094	chisq	All Patients
Age at consent	66.8 (12.6)	64.8 (10.7)	0.141	t-test	All Patients
Screen failed	22 (26.5%)	140 (49.1%)	<0.001	t-test	All Patients
Screen failed	22 (26.5%)	84 (36.7%)	0.094	chisq	Patients who completed biopsy requirement if applicable (n=83 and n=229)
Days until screen fail or intervention	24.7 (35.8)	36.7 (32.0)	<0.001	Wilcox on	All Patients, days until either screen fail or intervention
Days from consent to screen fail	44.3 (63.0)	35.9 (35.7)	0.192	Wilcox on	Only in patients who screen failed (n=22 and n=140)
Days from consent to intervention	17.7 (13.2)	37.5 (28.0)	<0.001	Wilcox on	Only in patients who did not screen fail (n=61 and n=145)
Days from consent to intervention	n/a	41.1 (27.6)	--	--	Only in patients who completed a biopsy and enrolled (n=104)
Days from consent to intervention	n/a	28.3 (27.3)	--	--	Only in patients with waived biopsy requirement who enrolled (n=41)
Screen fail due to performance status	3/22 (13.6%)	13/23 (56.5%)	0.005	Fisher's	Biomarker eligible patients
Biopsy status:			--	--	Only relevant to biopsy required patients
-Completed	0 (0%)	154 (54%)			
• Biomarker eligible		118 (77%)			Only completed biopsies
-Not completed	0 (0%)	56 (19.6%)			
-Not required	83 (100%)	0 (0%)			
-Waived	0 (0%)	75 (26.3%)			

**Table 3.** Multivariable (GEE) logistic regression model predicting screen fail for all patients

Patient Characteristics	Odds ratio (95% CI)	p-value
Biopsy Required (ref=not req)	2.87 (1.33-6.25)	0.007
Age	1.25 (1.05-1.48)	0.014
Gender (ref=male)	1.11 (0.89-1.37)	0.361
Site (random effect)	--	--