Abstract:
Somatic activating mutations in EGFR are present in 15–20% of non-small cell lung cancers (NSCLC). The EGFR tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib, and afatinib have each demonstrated significant improvement in progression free survival compared to standard platinum doublet chemotherapy when used in the first line setting. Despite this advance, tumor resistance to EGFR TKI treatment is a major clinical challenge. 20–30% of patients exhibit innate resistance and fail to respond to initial treatment. Moreover, 98% of patients who respond to initial EGFR TKI treatment exhibit incomplete responses. The third generation EGFR TKI, rociletinib, has shown efficacy against lung cancers harboring the EGFR T790M mutation, a common mechanism of acquired resistance to first and second generation EGFR TKIs. However, even in patients whose tumors harbor EGFR T790M mutations the objective response rate (ORR) is only 50–60% and complete responses are rare. This incomplete response to treatment results in residual disease that enables the eventual emergence of acquired resistance in patients, often a lethal event. I investigated signaling events that occur in response to EGFR oncogene inhibition in NSCLC cells to enable their adaptation and survival during initial therapy and found that NF-kappaB (NF-kB) signaling is rapidly engaged upon initial EGFR inhibitor treatment to promote tumor cell survival and residual disease. Co-occurring oncogenic events may also play a role in driving incomplete responses. My hypothesis is that treatment of EGFR-mutant lung cancers with rociletinib results in incomplete responses driven by NF-kB pathway activation and additional concurrent tumor genomic oncogenic events. I will test this hypothesis in the following Specific Aims:
Aim 1: Identify mechanisms of de novo resistance and incomplete response to rociletinib in patients with advanced-stage EGFR-mutant lung cancer.
Aim 2: Evaluate tumor adaptive survival mechanisms in response to rociletinib in a phase II window of opportunity clinical trial for patients with early stage EGFR-mutant lung cancer.
This will allow us to define adaptive mechanisms of incomplete response to rociletinib and in turn define rational companion therapies that when combined with rociletinib could result in more complete and durable responses for patients.
Human Use? Yes
Assurance Status Approved
Assurance Number [redacted]
IRB Expiration Date [redacted]

Animal Use? No
Assurance Status
Assurance Number
IACUC Expiration Date

Human and Animal Use Assurances:
SPECIFIC AIMS

Specific Aim #1: Identify mechanisms of de novo resistance and incomplete response to rociletinib in patients with advanced-stage EGFR-mutant lung cancer. I will perform whole exome, transcriptome and IHC analysis on patient biopsy specimens and determine whether elevated NF-kB activity or co-occurring oncogenic somatic mutations correlate with decreased ORR and PFS in patients treated with rociletinib.

Specific Aim #2: Evaluate tumor adaptive survival mechanisms in response to rociletinib in a phase II window of opportunity clinical trial for patients with early stage EGFR-mutant lung cancer. Patients will be treated with rociletinib prior to surgery and evaluated for pathological response. Molecular analyses will be performed on surgical resection specimens to assess for mechanisms of incomplete response.

Specific Aim #3:

Specific Aim #4:

Specific Aim #5:
## PERSONAL STATEMENT

<table>
<thead>
<tr>
<th>Impact of award on applicant's career</th>
<th>This award will be critical to my career development. As a physician-scientist my goal is to be at the forefront of translating basic science discoveries into novel treatments for cancer patients. I have a particular interest in thoracic oncology, and will focus my efforts on developing novel therapies for lung cancer patients. My long-term goal is to develop a research program aimed at identifying novel molecular therapeutic targets for translation into new therapies for lung cancer patients through investigator initiated clinical trials. This award will provide me with the necessary protected research time to develop an independent lung cancer research program. In addition, I will take advantage of the tremendous training opportunities at [ ] and beyond to continue to augment the skills necessary to become a leader in translational lung cancer research. This will include training in genomic analysis as well as clinical trial development.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other funding sources</td>
<td>There is partial overlap between this research proposal and the following research proposals that I have submitted or will submit:</td>
</tr>
<tr>
<td>1. CDMRP Lung Cancer Research Program Career Development Award entitled: [redacted]</td>
<td></td>
</tr>
<tr>
<td>2. Burroughs Wellcome Fund Career Awards for Medical Scientists Program Application entitled: [redacted]</td>
<td></td>
</tr>
<tr>
<td>Percentage time on research activities</td>
<td>For the duration of this grant I will have a minimum of 50% protected time dedicated to research activities.</td>
</tr>
<tr>
<td>Collection and analysis of data</td>
<td>As the PI of the study, I will oversee all aspects of the research including patient clinical trial enrollment, tissue collection and storage, database maintenance, RNA and DNA extraction, next generation sequencing library preparation and analysis, and IHC analysis. I will oversee clinical research coordinators in the proper collection of patient clinical response and safety data, as well as tissue collection and storage. DNA and RNA extraction and library preparation will be performed by technicians in the lab of my mentor [redacted], supervised by me. Next generation sequencing will be performed in the [redacted] center for advanced technology. Sequencing analysis will be performed by a [redacted] lab bioinformaticist with frequent input on the biological context of the data from me. Clinical trial data will be collected by clinical research coordinators and analyzed by me. I will be responsible for assembling the analyzed data and submitting a manuscript for publication.</td>
</tr>
<tr>
<td>Applicant's role</td>
<td>I have and will design all experiments related to the study. I will perform or directly supervise each of the experiments as well as analyze data in collaboration with a bioinformaticist employed by my mentor. I will be responsible for interpreting the data within the context of the lung cancer research field, as well as preparing and submitting manuscripts for</td>
</tr>
</tbody>
</table>
publication, and presenting the data at national and international conferences. My mentor will provide funding for the project in terms of reagents and research technicians and bioinformaticist salary support. He will also provide advice in terms of thoughtful review of manuscripts and presentations related to the project.

<table>
<thead>
<tr>
<th>Clinical potential of research project</th>
<th>The studies in my proposal have immediate clinical implications because they have the potential to demonstrate how characterization of genomic heterogeneity in lung cancer could serve as an improved prognostic and predictive biomarker for patients. I predict that in the next 5 years, the results from this research will lead to the development of a rigorous and quantitatively robust clinical grading system in which patient pretreatment tumor genomic complexity, as determined by deep sequencing, will predict response and resistance to EGFR targeted therapy. Furthermore, I predict that biomarkers of NF-κB activity in the form of immunohistochemistry or gene expression signatures will serve to predict which patients are likely to have a poor response to EGFR TKI treatment, including 3rd generation EGFR TKIs. Ultimately, this will identify patients with high risk of early progression on single-agent EGFR TKI therapy who would benefit from rationally designed targeted combination therapy that targets not only the dominant oncogenic EGFR-mutation, but also EGFR bypass pathways that have been activated either prior to or during EGFR TKI treatment by genomic or epigenetic events. This in turn will lead to the development of clinical trials to assess the safety and efficacy of rationally designed combination therapies that could lead to deeper and longer lasting responses and improved overall survival for patients. Beyond EGFR mutant lung cancers, I predict that this principle will be applicable to preventing resistance that is likely to develop against all current and future targeted therapies available for the treatment of lung cancer. This has the potential to turn subsets of metastatic lung cancer into chronic and manageable, rather than uniformly fatal, diseases. This in turn would improve the health and welfare of the U.S. population as a whole.</th>
</tr>
</thead>
</table>

| Applicant's career plan | As a physician-scientist my goal is to be at the forefront of translating basic science discoveries into novel treatments for cancer patients. I have a particular interest in thoracic oncology, and will focus my efforts on developing novel therapies for lung cancer patients. My long-term goal is to become a leader in translational lung cancer research at [XXXX] working towards finding new therapies for lung cancer patients. In this position, I will develop a research program aimed at identifying novel molecular therapeutic targets for translation into new therapies or combination therapies for lung cancer patients through investigator initiated clinical trials. |

<table>
<thead>
<tr>
<th>Sources of salary support</th>
<th>My current sources of salary include 25% clinical effort, as well as the following research funding:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>[XXXXX]</td>
</tr>
<tr>
<td>2.</td>
<td>[XXXXX]</td>
</tr>
<tr>
<td>3.</td>
<td>[XXXXX]</td>
</tr>
<tr>
<td>4.</td>
<td>[XXXXX]</td>
</tr>
<tr>
<td>5.</td>
<td>[XXXXX]</td>
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</table>
## Project Timeline

<table>
<thead>
<tr>
<th>Milestone/Activity</th>
<th>Description</th>
<th>Expected Date</th>
<th>Deliverable?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain IRB-approval and open clinical trial</td>
<td>I will write the investigator initiated study: &quot;....&quot;, receive IRB approval, and open the study for accrual at .... and the ....</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Complete RELA IHC on pre-treatment samples 1-25</td>
<td>RELA IHC will be preformed on pre-roclentinib treated samples and nuclear RELA staining will be scored and correlated with patient ORR and PFS to roclentinib.</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Complete RNA-Seq analysis on samples 1-25</td>
<td>RNA sequencing and gene expression analysis will be performed on patient samples 1-25. NF-kB signature will be correlated with patient ORR and PFS to roclentinib.</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Complete exome sequencing analysis on samples 1-25</td>
<td>Whole exome sequencing and analysis will be performed on patient samples 1-25. The presence of concurrent oncogenic mutations will be correlated with patient ORR and PFS to roclentinib.</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Accrue patients 1-10 to clinical trial</td>
<td>We will accrue the first 10 patient to the clinical trial: A phase II trial to evaluate Roclentinib induction therapy in patients with surgically resectable, EGFR-mutant non-small cell lung cancer, and evaluate their pathological response to roclentinib (primary endpoint).</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Complete RELA IHC on samples 26-50</td>
<td>RELA A IHC will be preformed on pre-roclentinib treated samples and nuclear RELA staining will be scored and correlated with patient ORR and PFS to roclentinib.</td>
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<td>No</td>
</tr>
<tr>
<td>Complete RNA-Seq analysis on samples 26-50</td>
<td>RNA sequencing and gene expression analysis will be performed on patient samples 26-50. NF-kB signature will be correlated with patient ORR and PFS to roclentinib.</td>
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<td>No</td>
</tr>
<tr>
<td>Complete exome sequencing analysis samples 26-50</td>
<td>Whole exome sequencing and analysis will be performed on patient samples 26-50. The presence of concurrent oncogenic mutations will be correlated with patient ORR and PFS to roclentinib.</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Milestone/Activity</td>
<td>Description</td>
<td>Expected Date</td>
<td>Deliverable?</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Accrue patients 11-27 to the clinical trial</td>
<td>We will accrue patients 11-27 to the clinical trial: &quot;\text{\textcolor{red}{\textbf{	extit{\textit{}}} \textbf{}} \textbf{}}&quot;, and evaluate their pathological response to rociletinib (primary endpoint).</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Submit abstract/present at ASCO annual meeting</td>
<td>I will submit an abstract and present data from &quot;\text{\textcolor{red}{\textbf{	extit{\textit{}}} \textbf{}} \textbf{}}&quot; to the 2019 ASCO Annual Meeting.</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Complete RNA-Seq and IHC analysis</td>
<td>RNA sequencing and gene expression analysis will be performed on pre-treatment and surgically resected specimens from the phase II neoadjuvant clinical trial. Increase in NF-kB activity will be correlated with patient pathological response rate to rociletinib.</td>
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# BUDGET SUMMARY

<table>
<thead>
<tr>
<th></th>
<th>Year1</th>
<th>Year2</th>
<th>Year3</th>
<th>Year4</th>
<th>Year5</th>
<th>Totals</th>
<th>Total All Years</th>
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<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>$11,543.00</td>
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<td>$8,541.00</td>
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<td>$2,500.00</td>
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<tr>
<td>Patient Care Costs (Outpatient)</td>
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<tr>
<td>Consortium/Contractual Costs</td>
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<th>Year3</th>
<th>Year4</th>
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<th>Totals</th>
<th>Total All Years</th>
</tr>
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<tbody>
<tr>
<td><strong>Indirect</strong></td>
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</table>

**Budget Totals**

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<th>Year3</th>
<th>Year4</th>
<th>Year5</th>
<th>Totals</th>
<th>Total All Years</th>
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</thead>
<tbody>
<tr>
<td>Direct Costs Total</td>
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<td>$66,666.00</td>
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<td>Indirect Costs Total</td>
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**Notes / Justification**

<table>
<thead>
<tr>
<th>Line Item</th>
<th>Note/Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel</td>
<td>Research Supplies: Principal Investigator) 20% (or 2.4 calendar months) effort and salary support from this project, is an assistant professor in the Department of Cancer Medicine. He has 10 years of experience performing basic and translational cancer research and is responsible for the preliminary data in the proposed application. As principal investigator, he will oversee all aspects of the proposed study. He will be responsible for the recruitment of patients under an IRB-approved protocol, performing DNA and RNA extractions, and preparing samples for the next generation sequencing, and immunohistochemical analysis. He will supervise the next generation sequencing data analyses in collaboration with a lab bioinformatician. We request $45,237 in support of Dr. 's salary and fringe benefits in year 1 and $46,228 in year 2, and $47,685 in year 3.</td>
</tr>
<tr>
<td>Supplies</td>
<td>Next Generation Sequencing: We will perform paired-end whole exome as well as RNA sequencing to a minimum depth of 100x per sample on a minimum of 100 human tumor samples using the Illumina HiSeq 4000 platform available through the lab. Library prep for each sample using the Illumina TruSeq DNA library preparation kit will be performed at a cost of $2,500 per sample. We will budget $14,088 in year 1, $13,045 in year 2, and $11,543 in year 3 towards these sequencing costs. Additional sequencing and other research costs not covered by this award will be covered by philanthropic gifts to the thoracic oncology research program or by Dr. 's institution.</td>
</tr>
<tr>
<td>Travel</td>
<td>Travel: Dr. will travel and present the results of the research funded by this grant at the ASCO annual meeting in each of the years funded by the grant. We request $2,500/year towards airfare, housing, conference registration, and abstract submission fees.</td>
</tr>
<tr>
<td>Other Expenses</td>
<td>Data Network Recharge: The data network service recharge provides funding for critical equipment in support of 's electronic information flow. Calculations are based on the percent effort to be charged to the project for each person named in the grant. Cost = $106 in year 1, $110 in year 2, and $113 in year 3.</td>
</tr>
</tbody>
</table>
Computing and Communication Device Support Services (CCDSS): CCDSS provides integral support to campus voice and data technology functions. CCDSS includes software installation/updates, internet security, hardware setup/configuration, and centrally managed patching, storage and backup. The university charges these expenses to all funding sources based on a monthly recharge rate per FTE, consistent with the university's current methodology used for data network services. The recharge rates are provided for under our approved DS-2, will be computed in accordance with applicable OMB requirements, including 2 CFR Part 220 (formerly Circular A-21), and will be reviewed and adjusted annually. 

Cost = $221 in year 1, $235 in year 2, and $235 in year 3.

GAEL Insurance: General Automobile and Employee Liability insurance costs are budgeted at composite rates of $0.0064 per salary dollar per University policy. We request $314 in year 1, $348 in year 2, and $390 in year 3.

<table>
<thead>
<tr>
<th>Indirect Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect Costs are established by a standard agreement with the Department of Health and Human Services. This project will be located On-Campus. It has a new F&amp;A rate agreement as of May 23, 2012; these are the on campus rate for instruction: July 1, 2015 and all subsequent years: 44.0%</td>
</tr>
</tbody>
</table>

Per the FOA, we are restricting this to $4,200 per year.
References Providing Letters of Support:

Mentor

Institutional Approver
<table>
<thead>
<tr>
<th>Title:</th>
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<tr>
<td>Status:</td>
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<tr>
<td>Funding:</td>
<td>Not Funded by the Conquer Cancer Foundation</td>
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<table>
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<td>Published</td>
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<tr>
<td>Funding:</td>
<td>Not Funded by the Conquer Cancer Foundation</td>
</tr>
</tbody>
</table>
Uploaded Documents:

- Biosketch
- Research Strategy – CDA
- Biostatistical Plan
- Cited References
- Advancing Patient-Focused Research
- Publication
- Clinical Protocol
- Supporting Documentation
- Supporting Documentation
- Supporting Documentation
- Supporting Documentation
- Institutional Letter of Support
Research Strategy
Significance and Background
Somatic activating mutations (Exon 19 deletion, Exon 20 insertion, G719A, S768I, V769L, T790M, L833F, L858R, L861Q) in EGFR are present in 15-20% of lung adenocarcinomas. The EGFR tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib, and afatinib have each demonstrated significant improvement in progression free survival compared to standard platinum doublet chemotherapy when used in the first line setting for advanced EGFR-mutant lung cancer. Despite this clinical advance, tumor resistance to EGFR TKI treatment is a major clinical challenge. Acquired resistance to first generation EGFR TKIs occurs within 9-12 months of initiating therapy. Moreover, 20-30% of patients exhibit innate resistance and fail to respond to initial treatment, while 98% of patients who do respond exhibit an incomplete response.

To date, efforts to understand the basis of EGFR TKI therapy resistance have largely focused on uncovering mechanisms of acquired resistance. A second site T790M resistance mutation in EGFR is hypothesized to account for the majority of acquired resistance that develops. Third generation EGFR TKIs (rociletinib and AZD9291) have shown efficacy against lung cancers harboring the EGFR T790M mutation. However, even in patients whose tumors harbor EGFR T790M, the objective response rate (ORR) is only 50-60% and complete responses are exceedingly rare. Similar to first and second generation EGFR TKIs, all patients eventually develop disease progression and succumb to their cancer. While mechanisms of acquired resistance to rociletinib and AZD9291 are being explored, the molecular basis of incomplete response and residual disease that occurs after initial 3rd generation EGFR TKI therapy is poorly understood.

Prior work has uncovered a cancer cell population termed 'drug tolerant persisters' that withstood initial treatment via an IGF1R-mediated epigenetic program that could be pharmacologically reversed with chromatin-directed or IGF1R targeted therapy. Subsequent clinical trials did not show a significant effect of either chromatin-directed or IGF1R targeted therapy on response to concurrent EGFR kinase inhibitor treatment in lung cancer patients. Although this hypothesis remains promising, additional studies are required. Other work exploring initial response to targeted therapy in cancer cells showed that EGFR inhibition provokes STAT3 survival signaling. I further investigated signaling events that occur in response to EGFR oncogene inhibition in lung adenocarcinoma cells to enable their adaptation and survival during initial therapy. I found that NF-kB signaling is rapidly engaged upon initial EGFR inhibitor treatment to promote tumor cell survival and residual disease. EGFR oncogene inhibition induced an EGFR-TRAF2-RIP1-IKK complex that stimulated an NF-kB-mediated transcriptional survival program (Figure 1). A recent study has also shown that NF-kB drives acquired resistance to the rociletinib analogue CNX-2006 in preclinical models. Validation of these findings in patients could unveil NF-kB activation as a critical adaptive survival

Fig. 1. Schematic depicting how NF-kB signaling is acutely activated in response to EGFR oncogene inhibition leading to downstream survival signaling through the IL6-JAK2-STAT3 pathway.
mechanism engaged by EGFR oncogene inhibition and provide rationale for EGFR and NF-kB co-inhibition to eliminate residual disease and enhance patient responses (Figure 1). Beyond adaptive NF-kB activation, pre-treatment tumor heterogeneity may in part explain incomplete responses to rociletinib. Sequist et al. found that the allele frequency of the EGFR T790M mutation correlated with increased response to rociletinib. This suggests that co-occurring events that bypass EGFR oncogene dependence could be driving incomplete response to therapy. Through whole exome sequencing (WES) I have identified co-occurring oncogetic mutations in PIK3CA27 and CTNNB1 (Beta-Catenin)28 present prior to rociletinib treatment in a patient with an EGFR T790M mutation who did not respond to rociletinib therapy after progression on erlotinib (Figure 2). Based on this background and preliminary data, I propose the following 

**Hypothesis:**

Treatment of EGFR-mutant lung cancer with the 3rd generation EGFR TKI rociletinib results in incomplete responses driven in part through NF-kB pathway activation and additional concurrent tumor genomic oncogenic events. I will test this hypothesis in the following **Specific Alims:**

**Aim 1:** Identify mechanisms of de novo resistance and incomplete response to rociletinib in patients with advanced-stage EGFR-mutant lung cancer.

**Aim 2:** Evaluate tumor adaptive survival mechanisms in response to rociletinib in a phase II window of opportunity clinical trial for patients with early stage EGFR-mutant lung cancer.

**Innovation**

The vast majority of research on EGFR TKI resistance has focused on acquired resistance after an initial response to therapy. This proposal is innovative in that it focuses on the problem of why responses to EGFR TKIs are almost always incomplete. It is this incomplete response to initial treatment that leads to residual disease that enables the eventual emergence of acquired resistance in patients, a lethal event. Understanding what drives these incomplete responses will be critical to improving long-term survival for EGFR-mutant lung cancer patients, by allowing for the development of rational combination therapies that lead to more frequent complete responses. By utilizing a window of opportunity clinical trial design this proposal is innovative in that it will allow us to study the biology of patient lung cancers early after exposure to EGFR TKI treatment. Such samples are rarely accessible as patients are frequently only biopsied after the development of acquired resistance.

**Approach**

**Aim 1:** Identify mechanisms of de novo resistance and incomplete response to rociletinib in patients with advanced EGFR-mutant lung cancer.

**1A.** Determine whether pre-treatment tumor NF-kB activation correlates with response to rociletinib treatment.

**Rationale:** Our prior studies demonstrated that NF-kB activation is associated with de novo resistance to EGFR TKI therapy in cellular and murine models of lung cancer.3,12 Identifying patients who may benefit the most from upfront combinations of EGFR and NF-kB inhibitors will be critical to developing rational combination therapy strategies. I hypothesize that patients with
evidence of pre-treatment NF-kB tumor activation will exhibit worse outcomes compared to patients with low NF-kB activity. Experimental Strategy: I am the site principal investigator for both the clinical trials to assess the safety of rociletinib in patients with advanced-EGFR-mutant lung cancer. We have accrued 20 patients to date on these trials, and expect to accrue 15-20 additional patients over the next year. Furthermore, FDA-approval for rociletinib use in the second line setting for EGFR-mutant lung cancer patients is expected in the next year given the overall positive results that have been reported. Utilizing an IRB-approved tissue banking protocol that I developed, I have consented and obtained biopsy material and blood from each patient that has been treated with rociletinib at the site. Over the 3-year period of this award I will obtain 50 patient biopsy specimens after progression on a first or second generation EGFR TKI, prior to rociletinib treatment.

To determine which downstream target genes of NF-kB are critical to its ability to promote tumor cell survival during EGFR TKI therapy, I performed whole transcriptome sequencing (RNA-seq) on genetically modified and NF-kB inhibitor treated EGFR-mutant NSCLC cell lines (see attached manuscript). Using these tools, I defined a signature of 36 NF-kB target genes in EGFR-mutant lung cancer cells, including established regulators of NF-kB signaling and cell survival such as TNFAIP3, BIRC3, and IL6.

On the basis of these findings, I examined the degree to which NF-kB activation is observed in EGFR-mutant lung cancer specimens from two EGFR TKI treated patients, the first whose best response was progressive disease, and the second who had a partial response to erlotinib treatment. I measured NF-kB activation by determining the levels of nuclear RELA as a biomarker of NF-kB activity in these specimens and found that while the EGFR-mutant lung cancer specimen from the patient with primary erlotinib resistance harbored abundant nuclear RELA (present in > 20% of tumor cells), the EGFR-mutant NSCLC specimen from the patient with partial response to erlotinib exhibited lower levels of nuclear RELA (present in < 10% of tumor cells; Figure 3A). To investigate whether the differences observed in nuclear RELA staining among the tumor specimens from these patients were indicative of NF-kB transcriptional activity, I performed RNA-seq analysis. Using the NF-kB signature that I defined in vitro (see attached manuscript), I found that 29 of 36 NF-kB target genes,
including IL6, were elevated in the NSCLC specimen from the patient with higher levels of nuclear RELA and primary erlotinib resistance compared to the NSCLC specimen from the patient with lower levels of nuclear RELA who responded to erlotinib (Figure 3B). Thus RELA nuclear staining and gene expression analysis of these 36 NF-κB target genes may be a reliable method to detect NF-κB activity in patient specimens.

To assess whether pre-treatment tumor NF-κB activation status correlates with response to rociletinib, I will perform RNA sequencing analysis and RELA IHC on 50 patient tumor specimens obtained prior to rociletinib treatment as described above. High NF-κB activity will be defined as both a positive NF-κB gene expression signature (determined by comparing the sum of the normalized transcripts per million (TPM) for each of 36 NF-κB target genes of interest (Figure 3) compared to RNA-seq data present in the TCGA database for lung adenocarcinoma, with patient samples that score in the top quartile of TCGA for these 36 genes defined as high NF-κB activity), and positive RELA nuclear staining in greater than 20% of tumor cells (as in Figure 3). I will determine whether pretreatment NF-κB activity is associated with the ORR (primary endpoint) or PFS (secondary endpoint) in rociletinib-treated individuals using the regression methods and statistical tests for binary (ORR) and survival (PFS) outcomes (see biostatistical plan for additional details).

Outcomes and alternative approaches: I predict that patients with evidence of high NF-κB activity in their tumors will exhibit decreased ORR and PFS to rociletinib treatment compared to those with low NF-κB activity. Due to tumor heterogeneity and contaminating cells of the tumor microenvironment, RELA nuclear staining in tumor cells may not be a reliable method to assess NF-κB activity. Furthermore, the RNA signature that I identified in 11-18 lung cancer cell lines 3 may not be broadly applicable to patient specimens. If I cannot validate the NF-κB gene expression signature in patient specimens with high RELA nuclear staining, I will explore alternative approaches to identify tumors with high NF-κB activity, including in situ hybridization, and Q-PCR for select NF-κB target genes including IL6, BIRC3, and TNFAIP3 as I have described 3. If no such correlation is found between tumor NF-κB activity and rociletinib treatment outcome, I will use whole exome sequencing (WES, see below) and RNA-seq analysis to generate alternative hypotheses that may explain poor or incomplete responses to 3rd generation EGFR TKI treatment.

Aim 1B: Determine whether pre-treatment tumor genomic alterations contribute to rociletinib resistance in patients with EGFR-mutant lung cancer.

Rationale: 40-50% of patients whose tumors harbor the EGFR T790M mutation do not respond to treatment with rociletinib 18. Furthermore, responses are almost always incomplete and short-lived with a median PFS of 10.3 months 18. Through WES of patient tumor specimens collected throughout the course of a patient’s disease, I have identified co-occurring oncogenic mutations in PIK3CA and CTNNB1 present prior to rociletinib treatment in a patient with an EGFR T790M+ lung cancer and acquired resistance to erlotinib, who did not respond to rociletinib treatment (Figure 2). I hypothesize that co-occurring oncogenic events present at the time of rociletinib treatment initiation drives incomplete and transient responses to therapy.

Experimental Approach: I will perform whole exome sequencing analysis on 50 EGFR-mutant lung cancer specimens collected prior to rociletinib treatment as described above. DNA will be extracted from tumors and matched normal tissue or blood (to be used as germline controls), and WES will be performed at a minimum depth of coverage of 100x. This will allow for the identification of somatic tumor genomic alterations to be reliably detected in as few as 10% of tumor genomic DNA 29,30. Under the guidance of my mentor Dr. [redacted], and through collaboration with bioinformaticists in his group, I will score pre-treated tumors based on the presence or absence of co-occurring somatic mutations and copy number alterations (CNA) in genes that have previously been shown to be involved in cancer as defined by the Catalogue of Somatic Mutations in Cancer (COSMIC) 31. Regression methods and statistical tests for binary and survival outcomes will be used to correlates the presence of pre-treatment tumor oncogenic
events with the ORR (primary endpoint) and PFS (secondary endpoint) clinical endpoints as described (See biostatistical plan for additional details).

Outcomes and alternatives: I predict that patients with tumors demonstrating pretreatment concurrent oncogenic somatic mutations or CNA will exhibit decreased ORR and PFS compared with patients with whose tumors harbor only EGFR mutations as their primary driver. Ultimately, I predict that patients with concurrent pretreatment oncogenic mutations will benefit from first-line rationally designed combination therapy that targets not only the dominant mutation (EGFR), but also the secondary genomic events that drive rociletinib resistance. I may not be able to achieve WES sequencing to the required depth on all specimens to low DNA quantity or quality. In specimens where this is the case, I will perform targeted sequencing of coding exons and selected introns of approximately 500 cancer-relevant genes developed at [redacted].

**Aim 2:** Evaluate tumor adaptive survival mechanisms in response to rociletinib in a phase II window of opportunity clinical trial for patients with early stage EGFR-mutant lung cancer.

**Rationale:** While pre-treatment activation of alternative pathways likely plays a role in rociletinib incomplete response, the role that early adaptive survival mechanisms play in promoting tumor cell persistence and residual disease in patients is unclear. I have shown that EGFR TKI treatment itself can lead to NF-kB activation and tumor cell survival using in vitro and in vivo models of NSCLC. Demonstrating this in patients will be critical to credentialing this pathway as a bona fide target to improve patient responses to 3rd generation EGFR TKIs. Access to patient tissue during the initial acute period of rociletinib treatment will be critical to defining the molecular mechanisms that underlie incomplete responses to EGFR TKI therapy. The availability of such tissue is incredibly limited, as EGFR TKI treatment is not standardly given prior to surgical resection of early stage lung cancers. Induction therapy with platinum-based chemotherapy given prior to surgical resection for patients with resectable lymph node-positive lung cancers is a safe and acceptable practice. The role of EGFR TKI treatment as induction therapy for patients with EGFR-mutant lung cancers remains incompletely explored. In an unselected study of 50 patients with stage I or II NSCLC treated with gefitinib, 17 of 21 patients found to have activating EGFR mutations in their resected tumor specimens had a radiographic response to treatment. In a separate study of an enriched population of 60 patients non-squamous with early stage lung cancer treated with erlotinib for 21 days prior to surgery, patients with EGFR activating mutations (n=7), 40% (3 of 7) had a pathological response with > 50% tumor necrosis at the time of resection. In contrast, only 20% (8 of 35 patients) with WT EGFR exhibited > 50% necrosis in their tumors at the time of resection. While these results suggest that neoadjuvant therapy may be beneficial to patients with EGFR-activating mutations prior to surgery, a prospective trial in pre-selected EGFR-mutant lung cancer patients has not been performed.

I hypothesize that neoadjuvant treatment with rociletinib, an EGFR TKI that targets T790M in addition to common activating mutations in EGFR, will improve patient responses to induction therapy. Furthermore, the neoadjuvant design of this trial will allow us to perform comprehensive molecular analyses on tumor specimens pre-treatment and after initial response to rociletinib.

**Aim 2A:** Assess the safety and efficacy of rociletinib as neoadjuvant therapy in patients with early stage EGFR-mutant lung cancer.

In collaboration with [redacted] (see letter of intent), [redacted] (see letter of collaboration), and [redacted] (see letter of collaboration), I will perform a phase II multi-institution, single-arm, open label clinical trial of neoadjuvant rociletinib in stage I-IIIA EGFR-mutant lung cancer patients who are planning to undergo surgical resection of their lung cancer (Figure 4). 27 eligible patients (see statistics section for data analysis and power calculations) will be treated with rociletinib for
approximately 28 days prior to surgery. The primary objective of the study will be to evaluate the efficacy of rociletinib as induction therapy in patients with surgically resectable EGFR-mutant lung cancer. The primary endpoint of the study will be pathological response rate defined as < 50% viable tumor present histologically in the resected tumor specimen. Secondary endpoints of efficacy will include: Objective response rate by RECIST 1.1 criteria, and metabolic response rate on paired FDG-PET scan (defined by PERCIST criteria). Secondary objectives of the study will be to evaluate the safety and tolerability of rociletinib using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0, and to evaluate tissue based biomarkers that may be predictive of response or primary resistance to rociletinib treatment.

**Aim 2B: Identify tumor adaptive survival mechanisms in surgically resected lung cancer specimens following rociletinib induction therapy.** I will perform RNA sequencing analysis on the patients for whom we will have pre-treatment tumor biopsy specimens, as well as tumor tissue acquired at the time of surgical resection (post-rociletinib). I will compare the gene expression of the 36 NF-kB signature genes that I previously defined (Figure 3). I will determine whether there is a statistically significant increase in NF-kB signature gene expression in the EGFR TKI resistance compared to the pre-treatment sample using established methods. To verify that NF-kB activity is increased in tumor cells, and not simply cells of the tumor microenvironment, I will perform RELA IHC on tumor specimens (as described above). Tumors that demonstrate an increase in RNA expression of NF-kB target genes and an increase in nuclear RELA expression will be scored as positive for NF-kB activation. I will compare pathological response rates in tumors that exhibit NF-kB activation post-rociletinib treatment compared to tumors that do not (see biostatistical plan for additional details).

**Outcomes and alternatives:** I predict that patients whose tumors exhibit an increase in NF-kB activity after rociletinib treatment will exhibit decreased pathologic response rates compared to patients without evidence of NF-kB activation. It is possible, however that tumors with high pretreatment NF-kB activity will not exhibit a significant change in NF-kB activity, but still may demonstrate poor outcomes in response to rociletinib treatment. If the RNA signature is not sufficient to identify patients with high NF-kB activity, I will employ alternative strategies to assess NF-kB activity as described above. Finally, alternative adaptive response pathways in response to rociletinib treatment may be responsible for tumor cell survival. I will assess RNA-seq data for alternative pathway activation using Gene Set Enrichment Analysis.

**Future Directions:** While outside the scope of this proposal, concurrent and future studies will include identifying pharmacologic approaches to overcome resistance pathways using patient-derived xenografts (PDX) and organoids derived directly from patients’ resected tumors as I have previously described. PDX-bearing mice will be treated with rociletinib or rociletinib in combination with therapies (acquired through commercial vendors) that targets putative resistance mechanisms identified, such as NF-kB. This will ultimately serve as the basis for future clinical trials testing rational combination therapies that can prevent or delay 3rd generation EGFR TKI resistance. I will also explore the role that NF-kB activity plays in cells of the tumor immune microenvironment (T-cells, NK-cells, B-cells, and macrophages) in promoting EGFR TKI resistance.
Biostatistical Plan:

**Aim 1A:** The primary objective of this aim is to determine whether high NF-κB activity in a patient’s tumor is associated with worse clinical outcomes in response to the EGFR inhibitor rociletinib treatment. The primary endpoint will be the patient ORR to rociletinib. Tumor NF-κB activity will be defined by high RELA nuclear staining (>20%) and a positive NF-κB gene expression signature defined as described in the Research Strategy. Sample size calculations are based on a one-sided, exact binomial test comparison of the observed ORR in patients with high NF-κB activity with a null-hypothesized ORR of 50%, which is consistent with the value observed in previous clinical trials with rociletinib in this patient population. We estimate that 50 patients will provide at least 85% power to detect a reduction in ORR to as low as 30% (i.e. a 20% reduction) as significant at the 5% level. The secondary endpoint will be PFS for patients receiving rociletinib therapy with pretreatment tumor NF-κB activity. Assuming a median PFS in treated patients without high activity of 10.3 months, an 18 month accrual period and 12 months of follow-up, 50 patients should provide 80% power to detect a 4 month decrease in median PFS (to approximately 6 months) in patients with high NF-κB activity. The observed ORR will be summarized as a proportion with an exact 95% confidence interval, and will be compared to the null hypothesized value of 50% using the approach described in the sample size justification. PFS will be summarized using Kaplan-Meier estimates, including an estimated median survival time with confidence limits.

**Aim 1B:** The primary objective of this aim is to determine whether the presence of pretreatment co-occurring oncogenic driver mutations in a patient’s lung cancer correlates with worse clinical outcomes in response to rociletinib treatment. The primary endpoint will be the association of patient ORR to rociletinib with the presence of co-occurring somatic mutations as described in the Research Strategy. Because we hypothesize a 20% reduction in ORR in patients with driver mutations compared to a reference value of 50% from other studies, the sample size calculations for Aim 1A apply here as well. The secondary endpoint will be the reduction in PFS among patients receiving rociletinib with co-occurring somatic oncogenic mutations. Based on the same assumptions about effect size and study design applied in the previous aim, we should retain 80% power for this aim as well. Analysis methods for this aim will mirror those described for Aim 1A.

**Aim 2A:** The primary objective of this aim is to evaluate the efficacy of rociletinib as induction therapy in patients with surgically resectable EGFR-mutant NSCLC. The primary endpoint of the study will be pathological response rate defined as < 50% viable tumor present histologically in the resected tumor specimen. As few as 20 evaluable patients will provide at least 80% power to detect a pathological response rate of 47% among patients receiving rociletinib induction therapy as significantly greater than an assumed null response rate of 20%, at the 5% significance level. With 27 patients, we will have 90% power to detect an increase of this magnitude as significant, and will retain 80% power to detect a treatment effect of as small as 27% in a two-sided comparison with the null hypothesized value of 20%. Analyses for this aim will be based on exact binomial tests and confidence limits.

**Aim 2B:** The primary objective of this aim is to determine whether an increase in tumor NF-κB activity correlates with pathological response rate to rociletinib induction therapy. The primary endpoint of the study will be change in NF-κB activity level as defined in the Research Plan. We will determine whether tumor increase in NF-κB activity level is associated with decreased pathological response to rociletinib. We assume that the observed response rate in patients with increased activity will be compared to an assumed null rate of 47% in patients with unchanged activity, using an exact binomial test with a one-sided alternative hypothesis. Results indicate that 27 patients will provide at least 80% power to detect a decrease as small as 23% as significant at the 5% level. Analyses will mirror those described for Aim 2A.
Cited References
Oncogenic driver mutations have been identified in > 50% of lung adenocarcinomas, with FDA-approved targeted therapies available for advanced EGFR and EML4-ALK-driven lung cancers. It is likely that therapies that target each of the known oncogenic drivers in non-small cell lung cancers (NSCLCs) (i.e. KRAS, NRAS, BRAF, RET, ROS1, PI3K, MET) will eventually be developed. However, responses to targeted therapies are likely to be short-lived due to de novo and acquired resistance. Treatment of NSCLC patients whose tumors harbor activating mutations in the kinase domain of EGFR (e.g. L858R, in frame Exon19 deletion), for example, with the EGFR tyrosine kinase inhibitor (TKI) erlotinib, leads to significant tumor regression in up to 70% of patients with minimal systemic toxicities. However, 30% of patients with EGFR activating mutations do not respond to EGFR TKI treatment, and the magnitude of tumor regression in patients that do respond is variable, almost never complete, and frequently short-lived with a median duration of 9-12 months. Thus inhibition of mutant EGFR by treatment with an EGFR TKI is not curative in the vast majority of EGFR-mutant lung cancer patients. In 60% of cases the primary mechanism of resistance is thought to be through a secondary mutations in EGFR. 3rd generation EGFR TKIs such as rociletinib have been developed that target secondary EGFR mutations, however patient responses remain incomplete and short-lived. Activation of parallel or downstream signaling pathway, such as MET, PI3K, BRAF, HER2, AXL, NF-kB, and ERK may contribute to the development of 3rd generation EGFR TKI resistance. How activation of these pathways evolves within the context of a human tumor, and the optimal strategies to overcome their activation, has not been determined.

I hypothesize that pretreatment tumor genome and transcriptome alterations, in the form tumor cell populations with concurrent genomic oncogenic alterations or survival pathway activation, such as NF-kB, impacts EGFR-mutant lung cancer response to rociletinib therapy. Furthermore, I propose that EGFR TKI treatment itself can induce the activation of NF-kB or other adaptive survival signaling pathways within cancer cells. This proposal will fully characterize how tumor genomic complexity and gene expression changes induced by EGFR TKI treatment affects response to EGFR targeted therapies in patients.

Broadly, my study aims to offer unprecedented fundamental insights into the function of genomic complexity and adaptive survival signaling and how they affect clinical response to therapy. The studies in my proposal have immediate clinical implications because they have the potential to demonstrate how characterization of genomic heterogeneity in a lung cancer could serve as an improved prognostic and predictive biomarker for patients. I predict that in the next 5 years, the results from this research will lead to the development of a rigorous and quantitatively robust clinical grading system in which patient pretreatment tumor genomic complexity, as determined by deep sequencing, will predict response and resistance to EGFR targeted therapy, including 3rd generation EGFR TKIs such as rociletinib. Furthermore, I predict that biomarkers of NF-kB activity in the form of immunohistochemistry or gene expression signatures will serve to predict which patients are likely to have a poor response to 3rd generation EGFR TKI treatment and benefit from upfront combination therapies.

The neoadjuvant clinical trial in my proposal to assess the safety and efficacy of rociletinib in EGFR-mutant lung cancer patients will provide us with unprecedented access to patient tissue after initial response to EGFR TKI treatment. Understanding how tumor cells persist to drive residual disease and ultimately disease progression will be critical to improving first line therapies for lung cancer patients, which in turn will improve patient long term survival.

Ultimately, this will identify patients with high risk of early progression on single-agent 3rd generation EGFR TKI therapy who could benefit from rationally designed targeted combination therapy that targets not only the dominant oncogenic EGFR-mutations, but also EGFR bypass pathways that have been activated either prior to or during EGFR TKI treatment by genomic or epigenetic events. This in turn will lead to the development of clinical trials to assess the safety
and efficacy of rationally designed combination therapies that could lead to deeper and longer lasting responses and improved overall survival for patients. Beyond EGFR mutant lung cancers, I predict that within 5 years this principle will be applicable to preventing resistance that is likely to develop against all current and future targeted therapies available for the treatment of lung cancer. This has the potential to turn subsets of metastatic lung cancer into chronic and manageable, rather than uniformly fatal, diseases. This in turn would improve the health and welfare of the U.S. population as a whole.

Conquer Cancer Foundation of ASCO
Career Development Award

Dear Committee Members,

I am writing this letter in support of Dr. [Redacted] application for the Conquer Cancer Foundation of ASCO Career Development Award entitled: [Redacted]

I am director of the Biostatistics Core [Redacted], and have worked previously with Dr. [Redacted] on the analysis plan for the investigator-initiated clinical trial described in his proposal: [Redacted]. I have also assisted Dr. [Redacted] in writing the statistical analysis plan for the other aims of his proposal.

I am delighted to collaborate with Dr. [Redacted] on this project, and look forward to continuing a productive collaboration with Dr. [Redacted] as part of the HDFCC.

Sincerely,
September 10, 2015

RE: Proposal for Investigator Initiated Trial

Dear Dr. [Redacted]:

Thank you for your proposal for the Investigator Initiated Trial (IIT) entitled [Redacted].

We are pleased to report that the [Redacted] Review Committee has approved your proposal, pending the submission to [Redacted] of a complete draft protocol, which is based on your proposal.

The IIT Review Committee has the following comments regarding the proposal:

1. Frequency of following plasma cfDNA needs to be determined and incorporated into the final budget: Given that [Redacted] doesn't work perfectly in patients with intrathoracic disease, there were questions raised about whether frequent testing would be worthwhile and cost effective.

2. As previously discussed, committee would like more detail provided regarding metabolic response endpoint (definition by persist criteria) and frequency of testing for PFS endpoint (the CT q 3 months, in the full protocol).

3. Clarification regarding who would be eligible for treatment with roc i in the adjuvant setting (responders meeting primary endpoint or investigator assessed?)

In support of this study, [Redacted] has agreed to provide you with the [Redacted] supply required for this study and funding in an amount that represents the standardized level of support for the resources required to manage the study. The funding that [Redacted] will provide is $19,706 per patient (27 patients) for a maximum total budget of $532,071.34.

[Redacted] maintains an internal protocol number tracking system; this study has been assigned Protocol Number [Redacted]. It is important that you use this number on all future correspondence with [Redacted].

This approval is conditional upon receipt from you of a draft protocol within the next 12 weeks. If this draft protocol is not received by [Redacted], you will receive a letter from [Redacted] with a specified date within which your protocol must be provided to [Redacted]. This approval will expire if your protocol is not received prior to that specified date.

To assist you in the protocol submission, we have included the following items:
1. Protocol Template. Please note that the language regarding Drug Handling, Dose Modification, and Serious Adverse Event (SAE) reporting must be included in the protocol to meet with our approval.
   NOTE: The protocol should be submitted to [Redacted] for review prior to Institutional Review Board (IRB)/Ethics Committee (EC) submission. Substantive changes following review may trigger committee re-adjudication.

2. Informed Consent Guidelines for Investigator-Sponsors of Studies with [Redacted] and ICF Template. The Guideline is a tool to assist you in meeting [Redacted] requirements for the Informed Consent Form (ICF). The template will provide you with the [Redacted] required language to include in your ICF. In addition, please note that the subjects' consent for the study must meet the requirements of all applicable laws and ethical standards.

3. IND Submission to the FDA. Please note that it is your responsibility to contact the FDA regarding the need for an IND for this study. If you like to request a cross-referencing letter from [Redacted] please contact [Redacted] to discuss. If an IND is not required, please send us documentation confirming that the study is IND-exempt. Included with this letter is the FDA Guidance for Industry: IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer.


5. Investigator Brochure (IB). We are including the IB and all IND safety submissions that have occurred since the document was published. At this time, you have been added to the regular distribution of safety notifications. Please ensure that all of these documents are submitted to your IRB/EC on an ongoing basis.
   NOTE: All future correspondence from [Redacted] regarding [Redacted] safety submissions will include the [Redacted] protocol number assigned in this letter. We recommend that you use this number when submitting documents to the IRB/EC.

[Redacted] will be working with you to facilitate the protocol and ICF submission to [Redacted]. Once completed, please send the draft protocol to [Redacted]. Prior to submission to the IRB/EC, the draft ICF you generate for this study should be sent to [Redacted].

We will then send any comments we may have on the draft protocol and draft ICF. Please do not submit to the IRB/EC until we provide feedback on these documents. Once you receive IRB/EC approval, please send a copy of the IRB/EC approved protocol, IRB/EC approval letter, and Curriculum Vitae and Medical License[s] of any investigators to [Redacted].

[Redacted] Note, we do not collect the IRB approved ICF unless we specifically request a copy of this document.

If you have any questions regarding the recommendations from the IIT Review Committee, please contact [Redacted] or [Redacted].

Thanks again for your interest. We look forward to hearing from you soon.
<IIT Program Director>
<Contact info>

cc: <MSL>
<Other>
Conquer Cancer Foundation of ASCO  
Career Development Award  

Dear Committee Members:

I am writing this letter in support of Dr. [Redacted] application for the 2016 Conquer Cancer Foundation of ASCO Career Development Award entitled: [Redacted]. I am an Associate Professor at the [Redacted] in the thoracic medical oncology program. I am delighted to collaborate with Dr. [Redacted] on this project and plan to open and accrue to the clinical trial described in his proposal: [Redacted].

After discussion and approval of this trial concept by our thoracic surgeons, I expect to accrue 5-10 patients to this study during the three year time period of this grant and will provide Dr. [Redacted] with access to clinical outcomes data and tissue from these patients for the comprehensive molecular studies described in his proposal. I am fully supportive of this concept and believe that it will provide us with a critical opportunity to understand why patients almost always have incomplete responses to EGFR tyrosine kinase inhibitor therapies. I look forward to continuing a productive collaboration with Dr. [Redacted] on this project.

Sincerely,

[Redacted]
September 1, 2015

Conquer Cancer Foundation of ASCO
Career Development Award

Dear Committee Members:

I am writing this letter in support of Dr. [Redacted] application for the 2016 Conquer Cancer Foundation of ASCO Career Development Award entitled: [Redacted]. I am a Professor and Chief of Thoracic Surgery at [Redacted], and director of the Thoracic Oncology Program within [Redacted]. I have worked closely with [Redacted] on research projects and clinical care over the past 5 years. I am delighted to collaborate with Dr. [Redacted] on this project and believe that we will readily accrue to the investigator initiated clinical trial described in his proposal: [Redacted].

We see over 500 new cases of early stage lung cancer per year at [Redacted] with a large proportion of them harboring EGFR activating mutations in their tumors. I expect that we will be able to fully accrue to this study over three year time period of this grant. I am fully supportive of the concept of induction therapy to treat early stage lung cancers and believe that it will provide us with a critical opportunity to understand why patients almost always have incomplete responses to EGFR tyrosine kinase inhibitor therapies. I look forward to continuing a productive collaboration with Dr. [Redacted] on this project.
Career Development Award

Re. __________________ – Conquer Cancer Foundation - Career Development Award

To Whom it May Concern,

It is with great pleasure that I write this institutional letter of support for Dr. __________________ application to the Conquer Cancer Foundation of ASCO’s Career Development Award for his project titled __________________. Dr. __________________ is a truly exceptional candidate. As Chief of the Division of Hematology and Oncology and Deputy Director and Director of Clinical Sciences in __________________, I am pleased to provide my full and unconditional support of Dr. __________________’s application. This award will give Dr. __________________ the additional support for what will clearly be an exceedingly successful academic oncology career.

Dr. __________________ came to us highly recruited out of the __________________ where he had completed training in the __________________ under the guidance of his research advisor Dr. __________________. Dr. __________________ had an outstanding graduate school career in which he published two first author, peer-reviewed publications, and was rated by Dr. __________________ as one of the top students that he had ever trained. During his first year of clinical training at __________________, Dr. __________________ exhibited excellent clinical proficiency and was well regarded by faculty and peers. Dr. __________________ has chosen to focus his clinical specialty on thoracic oncology where he continues to excel.

I have known Dr. __________________ for nearly 6 years, during his tenure in the Hematology/Oncology Fellowship and as a junior faculty member at __________________. Dr. __________________ will be mentored by Dr. __________________, himself an exceptional translational investigator in our lung cancer program. Dr. __________________’s research ability continues to stand out. He spent two years of his fellowship in Dr. ________________ laboratory where he made significant original contributions towards understanding how tumor-associated macrophages promote malignant mesothelioma growth and resistance to standard chemotherapy. Dr. __________________ has demonstrated a strong understanding of the research literature and a natural ability to organize and present scientific data. While he made significant discoveries in Dr. __________________ laboratory, she decided to leave __________________ for an outside opportunity. Dr. __________________ took this in stride and indeed has used this as an opportunity to develop an original research proposal which he has carried out in the laboratory of Dr. __________________. Dr. __________________ joined the faculty of the Division of Hematology and Oncology in __________________ and
was recently promoted to Assistant Professor. We are delighted that he has chosen to continue his career at [Name].

Dr. mentorship plan will consist of 1) mentorship from established and experienced clinical investigator, 2) involvement in a dynamic established Thoracic Oncology Program, and 3) additional institutional resources for further training in clinical research. Dr. will meet with his mentor in weekly meetings supplemented with additional conferences, including one devoted to clinical and translational research methodology, a second about current clinical research issues in thoracic oncology, and a third journal club. Dr. will be actively engaged in the clinical research endeavors of the Thoracic group and will be able to develop his research agenda in the context of a well-seasoned clinical trials unit including ample support from clinical research coordinators, regulatory affairs, contracts and grants, biostatistical, informatics, pharmacy and research nursing personnel. Dr. will also have access to [Name], which has provided training in the methods of clinical research for nearly 20 years. This program, which includes over 75 faculty members who are actively involved in clinical research and who participate as instructors in courses, offers diverse structured education with topics including epidemiology, statistics, molecular methods in clinical research, informatics, outcomes research, phase I/developmental research, research in underserved populations, decision and cost-effectiveness analysis.

The Division of Hematology/Oncology is committed to providing Dr. at least 50% time to complete this project and to helping Dr. turn the proposal he develops into a clinical trial. The Thoracic Oncology Program has a sizeable cohort of patients undergoing treatment for advanced, EGFR-mutant non-small lung cancer and accrual to this project will not be an issue.

Given Dr.’s early proven track record, his potential, and the programmatic and institutional strengths, it seems to us that Dr. is perfectly poised to take advantage of the opportunities afforded him by the 2015 Conquer Cancer Foundation of ASCO Career Development Award. In sum, I recommend him enthusiastically and without reservation. Using NIH academic descriptors, he is truly "exceptional."

Please do not hesitate to contact me with questions or concerns.
DOCUMENTS UPLOADED BY A REFERENCE:

Letter of Support
Biosketch
Re: Support for the application of

Conquer Cancer Foundation of ASCO
Career Development Award

Dear Committee Members,

I am writing this letter in support of Dr. [redacted] application for the 2016 Conquer Cancer Foundation of ASCO Career Development Award entitled: [redacted] [redacted] is a newly appointed Assistant Professor at [redacted] and meets the eligibility criteria of being within the first three years of his first full-time faculty appointment. [redacted] developed this proposal completely on his own with minimal advice and input from me. [redacted] has the full support of the [redacted] department of medicine, division of hematology/oncology and access to superb facilities and resources to carry out the proposed study. I have and continue to serve as [redacted] primary research mentor, helping guide [redacted] as he conducts translational research in the Thoracic Oncology program. [redacted] will receive the mandated protected time for his research and career development should he receive this award. I believe that [redacted] has outstanding qualifications and potential for a highly successful research career focused on the molecular pathogenesis of lung cancer and improving outcomes for lung cancer patients. He has my enthusiastic support for his application that I am confident will allow him to launch his fully independent career as a physician scientist and leading translational lung cancer researcher.

He has assembled a strong team of collaborators to accomplish the proposed translational research project, which I believe is potentially paradigm shifting in the field.

[redacted] began full-time work in my laboratory three years ago. I have been extremely impressed by him during this time and believe that he has strong potential for a career as an independent translational investigator. [redacted]’s research tackles some of the most important issues in cancer biology and clinical care in the precision medicine era: (1) defining key mechanisms of resistance to targeted cancer therapy and strategies to overcome resistance in lung cancer patients and (2) the role of genomic heterogeneity in lung cancer initiation, progression, and drug resistance. His translational research spans multiple disciplines, from clinical observation and data analysis, patient tumor molecular and genetic analysis, to laboratory-based cell and molecular mechanistic studies. This is evidenced by two projects led by him, one of which was recently published (with [redacted] as first-author) in [redacted]. In this study, [redacted] discovered that adaptive activation of NF-kB signaling is a key mechanism by which EGFR-mutant lung cancers escape from EGFR targeted therapy. [redacted] is now extending this work to further study the function of NF-kB in targeted therapy response in patient cohorts at [redacted]. These studies are all a prelude to a clinical trial testing the combination of an EGFR-inhibitor with an NF-kB inhibitor to enhance response in patients that [redacted] plans to lead in the near term. Thus, [redacted] focused on bridging the translational gap from mechanistic discoveries to clinical impact to improve outcomes for patients with unmet need, many under his care.
A second major project is leading pertains to the role of tumor genetic heterogeneity in lung cancer initiation, progression, and drug resistance. This project is an extension and parallel to the aforementioned studies on NF-kB and EGFR targeted therapy resistance. has led an IRB-approved tumor biopsy protocol wherein advanced-stage lung cancer patients are biopsied both at diagnosis and on treatment, including at treatment resistance (longitudinal tumor sampling). This effort has created a substantial resource to understand the role of major and minor genetic clones that are present in these cancers and clinical response to therapy and outcomes. has collaborated with members of my group and beyond to conduct whole exome sequencing and transcriptome in each of these tumors longitudinally acquired from the patients to understand the molecular landscape of the tumors and its evolution on therapy in patients. I believe this project is ideal translational study bridging bench to bedside that will propel to the forefront of the translational cancer research field rapidly.

's proposal focuses on a critical clinical question in lung cancer: why are tumor responses to 3rd generation EGFR TKIs incomplete? This is a key knowledge gap, because it is these residual tumor cells persisting after initial EGFR TKI treatment that underlie incomplete response and, ultimately, drive tumor drug resistance and patient death. To better understand why tumor cells survive EGFR TKI treatment, has proposed a neoadjuvant “window of opportunity” clinical trial to treat early stage EGFR-mutant lung cancer patients with the 3rd generation EGFR TKI rociletinib. This trial is innovative in its design, and will allow us to answer questions as to how tumors initially respond to and survive EGFR TKI treatment, which will be critical to identifying companion targets to enhance patient responses and long-term survival. has done a tremendous job of garnering the support of key players to make this trial successful, including: 1. who will provide the drug and fund the clinical trial, 2. and 3. external clinical collaborators who will accrue patients to the study. This trial has the full support of the lung cancer community, and indeed was touted as a model for how to move the field forward during the plenary session. I think that and this project have tremendous potential, and he has my full and enthusiastic support.

I am an Associate Professor (promoted 2 years early) and my laboratory has been operative for over 4 years. I believe is well supported under my mentorship. I have successfully mentored 2 clinical fellows into assistant professor positions (including ), 2 post-doctoral fellows into senior scientist positions within the biotechnology industry, and 1 graduate student through his PhD. My research group is currently composed of 14 members, including 3 full time technicians, 7 post-doctoral fellows (including 4 other physician scientists in training), 2 graduate students (including one MSTP student), a cancer bioinformatician, and a dedicated administrative assistant. Several post-doctoral fellows and both students in my lab have received highly competitive extramural grant funding under my mentorship. My laboratory is well funded because we have been fortunate to obtain extramural support from both philanthropic foundations and also NIH. My funding will cover any additional costs incurred by proposal that are not covered by this award. Thus, will conduct the proposed research in a stimulating and supportive environment. We are well positioned to translate our lab findings into the clinic because and I both independently care for lung cancer patients in the thoracic oncology clinic at weekly.

As his mentor, I will closely monitor's training and progress throughout the duration of the grant period. will participate and present his work at weekly research meetings, which will allow him to receive frequent feedback on his overall research plan. In addition, and I will meet at least monthly to discuss research results and how to continue his career development. will also present his work at a monthly thoracic oncogenome research meeting, which is attended by thoracic oncologists, thoracic surgeons, radiation oncologists, as well as clinical and basic scientists. In this interdisciplinary forum his research will be evaluated for its
translational potential by the thoracic disease management team. He will submit abstracts for presentation at appropriate national or international meetings. It is expected, and to publish 1-2 original manuscripts/year in premier scientific journals. In addition, he will take advantage of formal training courses in clinical trial design and genomic analysis.

In summary, Dr. [redacted] is an outstanding candidate for this Conquer Cancer Foundation of ASCO Career Development Award. He is a budding leader and star. He has a very strong research track record and I have no doubt that he will be successful in his planned endeavors. I strongly believe that this grant award will serve to catapult him forward in a world-class, supportive training environment here at [redacted]. This will allow [redacted] to continue his development as a fully independent investigator and a leader in translating scientific discoveries into new, more effective therapies for lung cancer patients. I believe [redacted] would be a tremendous ambassador of the Conquer Cancer Foundation of ASCO should he receive this prestigious award.

Please do not hesitate to contact me with questions.

Sincerely,

[Signature]

[Name]
Institutional Approval Face Sheet