Lung Master Protocol, a Phase II/III Study for Second Line Therapy of Advanced Squamous Lung Carcinoma
Re-thinking clinical trial design for NSCLC

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Strategies for Integrating Biomarkers into Clinical Trial Designs for NSCLC

Evolution of NSCLC → Histologic Subsets → Biomarker subsets

Improving the drug development process

- Less than 5-10% of drugs for oncologic diseases that enter phase 1 clinical trials successfully reach the end of phase 3 trials.
- How can we improve these rates?

- Adopt rigorous experimental randomized designs at the animal testing phase.
- Smaller uncontrolled phase I clinical trials, consider early randomized studies at phase 1 and phase 2 phases.
- Choose smaller biomarker-driven groups with higher plausibility that a match biomarker-drug pair will be confirmed.
- Apply power of genomics in patient selection.
- Expedite companion diagnostic development with more flexible and broad platforms.
Evolution of Identification of Genomic Alterations

1984 - 2003

No known genotype

KRAS

EGFR

ALK

PIK3CA

2004

No known genotype

KRAS

EGFR

ALK

PIK3CA

BRAF

HER2

ROS1

2009

No known genotype

KRAS

EGFR

ALK

PIK3CA

BRAF

HER2

ROS1

2014

No known genotype

KRAS

EGFR

ALK

PIK3CA

BRAF

HER2

ROS1

Lung Adenocarcinoma

1984 - 2003

No known genotype

KRAS

EGFR

ALK

PIK3CA

BRAF

HER2

ROS1

Lung squamous cell cancer

2012

TP53

CDKN2A

PTEN

PIK3CA

KEAP1

MLL2

HLA-A

NFE2L2

NOTCH1

RB1

Emphasized critical need for a public clinical trials system

4 goals for modernization with 12 recommendations

- Improve speed & efficiency of trial development & activation
- Incorporate innovative science and trial design
- Improve prioritization, support, and completion of trials
- Incentivize participation of patients and physicians

NCI is implementing a comprehensive approach to transforming its clinical trials system to create a highly integrated network that can address rapid advances in cancer biology based on:

- Recommendations from the IOM Report
- Previous reports (Clinical Trials & Operational Efficiency)
- Current stakeholder input
Umbrella

Test impact of different drugs on different mutations in a single type of cancer
• BATTLE
• I-SPY2
• SWOG Squamous Lung Master

Basket

Test the effect of a drug(s) on a single mutation(s) in a variety of cancer types
• Imatinib Basket
• BRAF+
• NCI MATCH
Rationale for Master Protocol Design

- **Multi-arm Master Protocol**
  - Homogeneous patient populations & consistent eligibility from arm to arm
  - Each arm independent of the others
  - Infrastructure facilitates opening new arms faster
  - Rolling phase II (PFS)/phase III (PFS/OS) design allows rapid drug/biomarker testing for detection of “large effects” – bringing safe and effective drugs to patients faster
  - FDA registration potential
  - Screening large numbers of patients for multiple targets by a broad-based NGS platform reduces the screen failure rate and allows a sufficient “hit rate” to engage physicians and patients—a treatment for almost every patient.
S1400 Master Protocol Unique Private-Public Partnerships with the NCTN
PHASE II/III BIOMARKER-DRIVEN MASTER PROTOCOL FOR SECOND LINE THERAPY OF SQUAMOUS CELL LUNG CANCER.

NCT #TBD

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STUDY AGENTS:

- AZD4547 (NSC 765338)
- Docetaxel (Taxotere®) (RP56976) (NSC-6286)
- Erlotinib (OSI-774, Tarceva®) (NSC-718781)
- GDC-0032 (NSC 778785)
- MEDI4735 (NSC 778709)
- Palbociclib (PD-0332991) (NSC 772256)
- Rilotumumab (AMG102) (NSC 750009)

Protocol IND#119672
IDE #G120222

BIOSTATISTICIANS:

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University of Ottawa

NRG
Jeff Bradley, M.D.
Washington University School of Medicine
**S1400: MASTER LUNG-1: Squamous Lung Cancer- 2nd Line Therapy**

Multiple Phase II-III Arms with "rolling" Opening & Closure

- **Biomarker Profiling (NGS/CLIA)**
  - **FGFR ampl, Mut, Fusion**
  - **CCND1, CCND2, CCND3, cdk4 ampl**
  - **PiK3CA Mut**
  - **C-MET Expr**

- **PI3Ki** → **CT***
  - Endpoint PFS/OS
- **CDK 4/6i** → **CT***
  - Endpoint PFS/OS
- **FGFRi** → **CT***
  - Endpoint PFS/OS
- **HGFi+E** → **E***
  - Endpoint PFS/OS

CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

Pl: V. Papadimitrakopoulou (SWOG)
Steering Committee Chair: R. Herbst (YALE, SWOG)
Lung Committee Chair: D. Gandara
Translational Chair: F. Hirsch
Statistical Chair: M. Redman
Lung-MAP: Major Goals and Hypothesis

• **Hypothesis:** Lung MAP will improve genomic screening and time lines for drug-biomarker testing allowing for inclusion of the maximum numbers of otherwise eligible patients in comparison with currently employed “single screen-single trial” approaches.

• **Ultimate goal** is to identify and quickly lead to approval safe and effective regimens (monotherapy or combinations) based on matched predictive biomarker-targeted drug pairs.
Study Design and Objectives

Design:
Independently conducted and analyzed parallel Phase II/III studies

Primary Objectives within each sub-study:

Phase II Component:
1. To evaluate if there is sufficient evidence to continue to the Phase III component by comparing progression-free survival (PFS) between patients randomized to investigational therapy versus SoC.

Phase III Component:
1. To determine if there is both a statistically and clinically-meaningful difference in PFS between the treatment arms.
2. To compare overall survival (OS) between treatment arms.
Objectives

• Secondary Objectives:

A) Phase II and III: 1. compare response rates among patients with measurable disease randomized to receive TT/TTC/NMT versus SoC. 2. Frequency and severity of toxicities with TT/TTC/NMT versus SoC

• Exploratory Objectives:

A) To identify additional predictive tumor/blood biomarkers that may modify response or define resistance to the TT beyond the chosen biomarker

B) To identify potential resistance biomarkers at disease progression

C) To establish a tissue/blood repository from patients with refractory squamous cell cancer.
Eligibility

- The patient has a diagnosis of pathologically confirmed lung SCCA by tumor biopsy and/or fine-needle aspiration.
- Patients must have progressed after receiving a platinum-based chemotherapy regimen.
  - Patients who received platinum-based chemotherapy for Stage I-IIIB disease may have received at most one additional chemotherapy regimen for Stage IV disease and must have progressed after receiving this regimen for Stage IV disease.
  - Patients who progressed after chemotherapy for Stage IV disease must not have received any additional chemotherapy.
- Measurable disease (subjects with active new disease growth in previously irradiated site are eligible).
- The patient’s performance status is ≤ 2 at study entry.
- The patient has adequate organ function (will be specified in detail in the full protocol).
- If patient has brain metastasis, they must have been stable (treated and asymptomatic) and off steroids for at least 2 weeks.
- *Drug-specific inclusion and exclusion criteria will be applied as appropriate for each sub-study.
## Eligibility Updates

<table>
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<th>Revised</th>
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<tr>
<td><strong>Disease setting</strong></td>
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<tr>
<td>Incurable stage IIIB or Stage IV</td>
<td>Only Stage IV</td>
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<tr>
<td>Mixed Histology ≥50% allowed</td>
<td>Mixed histology not allowed</td>
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<tr>
<td><strong>Prior Treatment</strong></td>
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<tr>
<td>No restrictions on prior radiation</td>
<td>Prior radiation within 28 days before S1400 registration not allowed</td>
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<td>Exactly one platinum-containing chemotherapy regimen</td>
<td>Platinum-based chemotherapy required.</td>
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<td></td>
<td>• Can be regimen for Stage I-IIIB</td>
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<td></td>
<td>• 2nd for Stage IV allowed after progression of Stage I-IIIB</td>
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<tr>
<td></td>
<td>• If initial chemo given for Stage IV, exactly one allowed</td>
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<tr>
<td><strong>Other</strong></td>
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<tr>
<td>Register to assigned sub-study within 28 days</td>
<td>Register to assigned sub-study within 42 days</td>
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<tr>
<td>SGOT/SGPT &lt;= 2.5</td>
<td>ALT/AST &lt;= 2.0</td>
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</table>
Patient-level Schema

- S1400 Consent Registration
- Assigned Sub-study by screening results
- S1400X* Consent Registration
- Investigational Therapy

Genomic Screening ≤ 16 days
Sub-study registration ≤ 28** days
1:1 Randomization

**Protocol amendment in Process to change to 42 days

Tumor Submission (w/in 24 hrs)

Central genomic screening (and IHC) Foundation Medicine NGS test platform (CLIA/CAP).

* X = A, B, C, D, or E
Lung-MAP Trial Schema

FMI NGS/MET IHC

Non-match
(Anti-PD-L1)

PI3K
PIK3CA mut

CDK4/6
CCND1, CCND2, CCND3, cdk4 ampl

FGFR
FGFR ampl, mut, fusion

HGF
c-Met Expr

1:1 1:1 1:1 1:1

Arm¹ Arm² Arm¹ Arm² Arm¹ Arm² Arm¹ Arm²

¹ Medi4736 ¹ GDC-0032 ¹ Palbociclib ¹ AZD4547
² Docetaxel ² Docetaxel ² Docetaxel ² Docetaxel

¹ Rilotumumab + erlotinib
² Erlotinib
Rationale-Science

Sub-study A

- MEDI4736 anti PD-L1 moAb.
- Prior evidence of activity of anti-PD1 and anti PD-L1 moAbs with a range of RR from 17% to 24% in unselected NSCLC cohorts.
- Promising preliminary clinical activity NSCLC, including SCCA.
- Safety profile favorable.
- Activity within PD-L1+ cohort a secondary objective.
Rationale-Science

Sub-study B

- GDC—0032 beta isoform-sparing PI3K inhibitor more potent against $PIK3CA^{\text{mut}}$ than wt in vitro, interacts with mutant p110α conformation.

- Promising preliminary clinical activity in $PIK3CA$ mutant cancers including SCCA.

- Safety profile c/w other PI3K inhibitors.
Sub-study C

- PD-0332991 orally active, highly selective inhibitor of cdk4/6.
- *In vitro* activity in Rb+ cell lines and xenografts.
- Best monotherapy activity in unselected population: SD.
- Drug very active in combination with letrozole in ER+, HER2- breast cancer.
Rationale-Science

Sub-study D

- AZD4547 potent and selective inhibitor of FGFR1, 2 and 3.
- *In vitro* activity in FGFR amplified, mut+, gene translocation+ cell lines.
- Best monotherapy activity FGFR amplified SCCA: PR.
- Mucosal dryness, eye, phosphate metabolism.
Sub-study E

- AMG102 Ab against HGF/SF, the only ligand of c-Met receptor
- EGFR and Met may cooperate in driving tumorigenesis.
- Met over expressed in up to 50% of NSCLC
- AMG102 in registration trial+CT in gastric cancer.
**Tissue Requirements**

1. Tissue block (preferred) or at least 12 five-micron unstained slides (20 slides are strongly recommended). – must contain 20% tumor cells.

2. Hematoxilyn-eosin (H&E)-stained slide or Aperio H&E-stained slide

3. Local pathology report from initial diagnosis

4. **S1400 Local Pathology Review Form:**
   Tumor material must be reviewed by a local pathologist to ensure sufficient tumor cells are present in the sample. The local pathologist must review and sign off on the S1400 Local Pathology Review form noting that the tumor tissue contains at least 20% viable tumor cells.
Pathology Review - Local Pathologist to Ensure:

1. Squamous Lung Cancer according to WHO, +/- IHC verification: p 40/p63 positive, TTF1 negative.

2. At least 20% viable tumor
   - It is strongly intended to obtain biopsy at time of PD for responding pts in order to study acquired resistance mechanisms,
   - Peripheral blood at screening and follow-up (plasma and buffy coat).

- EXPLORATORY STUDIES: Applications through regular SWOG TM mechanisms. (www.swog.org)
Squamous Lung Master Protocol Clinical Trial Assay Based On Foundation Medicine NGS Platform

Foundation Medicine NGS test platform (CLIA/CAP)

1) DNA extraction
2) Library construction: selected cancer genes
3) Analysis pipeline

Classification rules

- Based on FM T5 NGS platform
- Implemented as “mask” of T5 content and classification rules on called alterations
- Rules determine biomarker positive/negative status

Classification rules (preliminary)

PIK3CA mutation
- PI3K inhibitor

CCND1, D2, D3 amplification, CDK4 amplification
- CDK4/6 inhibitor

FGFR1/2/3/4 amplification, mutation or fusion
- FGFR inhibitor

Non-NGS biomarkers:

Supplementary assays
- MET IHC (+)
- MET pathway inhibitor

Non-match arm
- All assays (-)
- Anti-PD-L1 Ab

LUNG-MAP
Tissue Flow / Reporting Flow

Tissue Acquisition at Site
Evaluation by Local Pathologist

Ship using Specimen Tracking System (STS)

Foundation Medicine Receives Specimen

FMI NGS

CLARIENT c-Met IHC (daily)

SWOG Statistical Center (daily)

Site Notified of Sub-study Assignment with Biomarker reports

Tissue Flow Reporting Assays are run in parallel
Study Design Within Each Sub-study

Phase II Analysis
55 PFS events

Phase III Interim Analyses
OS for efficacy
PFS/OS for futility

Complete Accrual

Final Analysis
256 OS events
290 PFS events

Futility established

Stop

12 months follow-up
### Statistical Design: Phase II Interim Analysis

Each sub-study can choose between Plan A or Plan B to determine “bar” for continuation past Phase 2 interim analysis.

<table>
<thead>
<tr>
<th></th>
<th>Plan A</th>
<th>Plan B</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>PFS</td>
<td></td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td></td>
<td>55 progression events</td>
</tr>
<tr>
<td><strong>Target HR (% improvement)</strong></td>
<td>HR = 0.5</td>
<td>HR=0.4</td>
</tr>
<tr>
<td></td>
<td>2-fold increase</td>
<td>2.5-fold increase</td>
</tr>
<tr>
<td><strong>Power</strong></td>
<td>90%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Type I error</strong></td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Approx. Threshold to continue:</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>HR % improvement</strong></td>
<td>HR= 0.71</td>
<td>HR = 0.61</td>
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<tr>
<td></td>
<td>41% increase</td>
<td>63% increase</td>
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</table>

LUNG-MAP
**Statistical Design: Phase III**

<table>
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<tr>
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<th>PFS and OS Co-primary</th>
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<tbody>
<tr>
<td></td>
<td>PFS</td>
</tr>
<tr>
<td>Events</td>
<td>290</td>
</tr>
</tbody>
</table>
| Null Hypothesis (HR) | 0.75*  
(33% improvement) | 1.0  
(equivalence) |
| Alternative Hypothesis | 0.5  
(2-fold increase) | 0.67  
(50% improvement) |
| Type I error (1-sided) | 0.014 against HR = 1.33  
< 0.00001 against HR = 1 | 0.025 |
| Power            | 90%                   | 90%             |

*Non HR = 1 null hypothesis encodes clinical significance*

Sample size based on OS for all studies
**Biomarker prevalence and overlap estimates (based on 108 sqNSCLC)**

<table>
<thead>
<tr>
<th></th>
<th>AZ/FGFR</th>
<th>Pfizer/CDK</th>
<th>Genentech/PIK3CA</th>
<th>Amgen/Met*</th>
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</thead>
<tbody>
<tr>
<td>AZ/FGFR</td>
<td>10.2%</td>
<td>2.8%</td>
<td>0.9%</td>
<td>2.0%</td>
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<tr>
<td>Pfizer/CDK</td>
<td></td>
<td>13.9%</td>
<td>1.9%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Genentech/PIK3CA</td>
<td></td>
<td></td>
<td>9.3%</td>
<td>1.9%</td>
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<tr>
<td>Amgen/Met</td>
<td></td>
<td></td>
<td></td>
<td>20%</td>
</tr>
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</table>

*Assumption of 20% prevalence for Met and random overlap between Met and other biomarkers*
## Sample Size for Active Sub-studies

<table>
<thead>
<tr>
<th>Sub-study ID</th>
<th>Prevalence Estimate</th>
<th>Sample Size Estimate</th>
<th>Decision Time Estimate</th>
<th>Sample Size</th>
<th>Study Duration</th>
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<tbody>
<tr>
<td>S1400A</td>
<td>56.0%</td>
<td>170</td>
<td>8</td>
<td>400</td>
<td>21</td>
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<tr>
<td>S1400B</td>
<td>GNE+</td>
<td>5.6%</td>
<td>78</td>
<td>288</td>
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<tr>
<td></td>
<td>FMI+</td>
<td>8.0%</td>
<td>152</td>
<td>400</td>
<td>72</td>
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<tr>
<td>S1400C</td>
<td>11.7%</td>
<td>124</td>
<td>11</td>
<td>312</td>
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<tr>
<td>S1400D</td>
<td>9.0%</td>
<td>112</td>
<td>11</td>
<td>302</td>
<td>53</td>
</tr>
<tr>
<td>S1400E</td>
<td>16.0%</td>
<td>144</td>
<td>9</td>
<td>326</td>
<td>37</td>
</tr>
</tbody>
</table>
Where are we now?

- Study Activated June 16, 2014
- As of October 27, 2014
- IRB Approvals:
  - 353 sites
  - 29 sites with at least 1 patient accrual
- Accruals:
  - 59 patients registered to S1400 (23 in last month)
  - 44 patients notified of their sub-study assignment
  - 19 patients registered to a sub-study

  - S1400A: 8
  - S1400B: 0
  - S1400C: 3
  - S1400D: 2
  - S1400E: 6
Key Aspects of Drug Selection

Sources:
- Investigator/Drug Selection Committee initiated,
- Pharmaceutical company initiated
- Solicited by RFA

Initial Qualification:
- Investigational drug/biomarker combination with preclinical & clinical data supporting safety & potential efficacy as a targeted therapy or “non-match” therapy in lung SCC
- Ready or near ready to enter the Lung-MAP phase 2 clinical protocol
Key Aspects of Drug Selection

- Candidates are evaluated by the Lung-MAP Drug Selection Committee (DSC), comprised of:
  - Key investigators & clinical researchers
  - Biomarker & molecular target experts from academia, NCI and FDA
  - Non-conflicted industry-based drug developers

- Candidates are scored based on:
  - Target appropriateness for Lung-MAP
  - Drug/Biomarker preclinical & clinical data
  - PK/PD data
Project Evolution

• Total Sample Size Projected over 5 years = 5,000
  (625-1250 screened/yr to accrue 500-1000/yr)
• New studies roll in in real-time (2 new in planning)
  - PARP inhibitor for BRCA-1, -2 mut
  - Combination immunotherapy for non-match Arm
    (anti-PD-L1+anti-CTLA4).
• Correlative science projects based on tissue/blood repository at SWOG.
**Novel Clinical Trial Designs for NSCLC**

Improving the drug development process

- **Biomarker-driven clinical trials require rigorous biomarker testing and validation.**
- Selecting genomic sub-sets with clear driver mutation designation is the right path but may prove to be challenging as clear drivers yet to be identified may be exceedingly rare.

- Complex genomic landscapes may require combination targeted therapy but preclinical models do not always directly translate in the clinical setting.

- Emergence of immunotherapy and potential immunotherapy combinations mandates definition of subsets that may benefit, biopsy-driven clinical trials to capture dynamic nature of immune checkpoint expression.

- Lessons learned from well designed clinical trials based on robust teams serve as the building blocks for future cures.
Thank you

- Hossein Borghaei, D.O. ECOG-ACRIN, Fox Chase Cancer Center (Sub-study A).
- Jeffrey A. Engelman, MD, Ph.D., ALLIANCE, Massachusetts General Hospital Cancer Center (Sub-study B).
- Corey J. Langer, M.D. NRG, University of Pennsylvania, Hematology Oncology Division, Abramson Cancer Center (Sub-study B).
- Martin J. Edelman, M.D., NRG, The University of New Mexico (Sub-study C)
- Kathy S. Albain, M.D. SWOG, Loyola University Medical Center (Sub-study C)
- Charu Aggarwal, M.D., M.P.H. ECOG-ACRIN, Abramson Cancer Center (Sub-study D)
- Primo N. Lara, Jr., M.D. SWOG, UC Davis Comprehensive Cancer Center (Sub-study D)
- Mark A. Socinski, M.D., ALLIANCE, Pittsburgh School of Medicine (Sub-study E)
- David R. Spigel, M.D., SWOG, Sarah Cannon Research Institute Sub-study E)
### Study Drug Management

#### Trial Starts
- **June 2014**

#### Timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
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### Data Management

#### Pre-Study Activities, Planning
- **Initial Meeting March 2013**
- **Drug Selection**
- **Protocol Development**
- **Assay Co. Selection**
- **Master IND application**
- **Master IDE application**
- **Approvals**
- **Contracts**

#### Project Management
- **Team Meetings, Teleconferences**
- **Other Activities**

#### Study Drug Management

#### Clinical Operations Management

#### Data Management
Screen for eligibility, consent patient and confirm that required amount of tissue is available for submission (pathologist to complete the Local Pathology Review Form)

Register to S1400 in OPEN

Submit tissue specimen within 1 day after registration (Ship to FMI and log shipment using the Specimen Tracking System)

Within 16 days after S1400 registration

Site staff receives email from SWOG with sub-study assignment (Assignment will also display in the Sub-study Assignment form in Rave®)
Post Sub-study Assignment

Evaluate common eligibility and sub-study specific eligibility criteria

If patient IS eligible for assigned sub-study

Register to sub-study in OPEN within 42 days of receiving sub-study assignment email to receive randomized sub-study treatment assignment

Administer protocol treatment within 7 working days of sub-study registration, conduct follow-up, obtain and submit specimens and forms per sub-study protocol
Funding Highlights

• Sites will receive up to $5,869 ($1,079 screening/$4,790 registration) for each patient on trial

• If biopsies are needed, sites will receive $3,000/$6,000 for the biopsies performed at screening and/or progression after initial response on Arm 1

• Sites will be reimbursed for additional research based procedures

• Sites will be reimbursed $1,333 for extra audit visits outside regular schedule
Funding Changes

FDA has requested tests/procedures to be performed on the investigational and standard of care arms. Sites will be reimbursed for the following additional procedures on both arms.

<table>
<thead>
<tr>
<th>Sub-study</th>
<th>Additional Funding for Procedure/Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1400A</td>
<td>TSH T3/T4*</td>
</tr>
<tr>
<td>S1400B</td>
<td>HbA1c, Lipase, Amylase</td>
</tr>
<tr>
<td>S1400C</td>
<td>EKG, HbA1c*</td>
</tr>
<tr>
<td>S1400D</td>
<td>OCT Scan, Ophthalmological Assessment, MUGA, Phosphate, Urinalysis, Troponin</td>
</tr>
<tr>
<td>S1400E</td>
<td>No changes</td>
</tr>
</tbody>
</table>

*This is an added test requested by the Company as part of the amendment*