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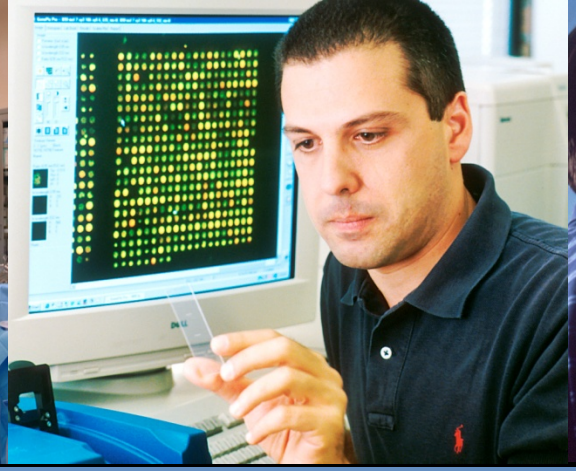
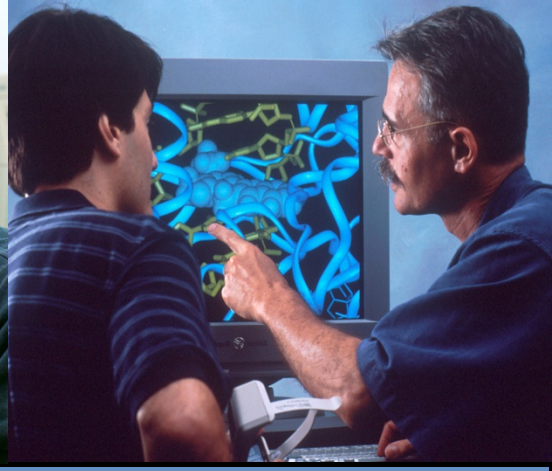

Genomic Clinical Trials: NCI Initiatives

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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NCI Precision Medicine Initiatives

- Help to advance molecular profiling from research use into the clinic
- Genotype to Phenotype
  - Develop portfolio of trials across spectrum from early stage to advanced disease
  - Screen for molecular features that may predict response to a drug with a given mechanism of action
  - Analyze tumor specimens at relapse to define mechanisms of resistance
- Develop public database that links clinical outcomes with molecular tumor characteristics

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NCI-Supported Genomic Clinical Trials: Overview

- ALCHEMIST: Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial
- SWOG1400: Biomarker-Driven Master Protocol for Second Line Therapy of Squamous Cell Lung Cancer
- M-PACT: Molecular Profiling Based Assignment of Cancer Therapeutics
- NCI-MATCH: Molecular Analysis for Therapy Choice:
  Dr. Barbara Conley
- Dr. Elizabeth Mansfield: FDA Division of Devices

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Lung Cancer Epidemiology in US

	New Cases / Yr	Deaths / Yr
Male	116, 470	87,750
Female	109,690	72,790
Total	226,100	160,340

Incidence/Mortality: ACS Cancer Facts and Figures/ SEER 2012

	Local	Regional	Distant	Unstaged
Stage at Dx	16%	22%	56%	7%
5 year survival	52%	24%	4%	--

Stage at Dx: SEER Cancer Statistics, 1999-2007
5-yr Survival: Adjusted for normal life expectancy & based on cases diagnosed in SEER 17 areas from 2001-2007 & F/U 2008

5 year survival after lobectomy (Stage IA, IB): 45-63%

5-yr survival for stage 1A and 1B NSCLC – Ou SH, et al, Cancer 2007, California Cancer Registry (19,702 pts) 1989-2003. Similar findings to Raz, DJ et al, Chest 2007: 54%.

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ALCHEMIST: Project Goals, Design, & Operational Assumptions

Goals:

- Conduct one integrated program for screening the target patient (regional disease) population to identify the patients with tumors with EGFRmut & ALK rearrangements for assessment for enrollment on either of 2 specific adjuvant trials testing the benefit of adding erlotinib or crizotinib to adjuvant therapy (respectively) combined with a research component for screened + and screened neg patients
- Define biologic/molecular progression of non-squamous NSCLC (both +/- screened pts)
- Evaluate two promising therapies in adjuvant setting targeted for specific molecular subsets of the disease
- Provide public resource for research community w/ genomic characterization tied to detailed clinical annotation, epidemiology data, & long-term outcome data

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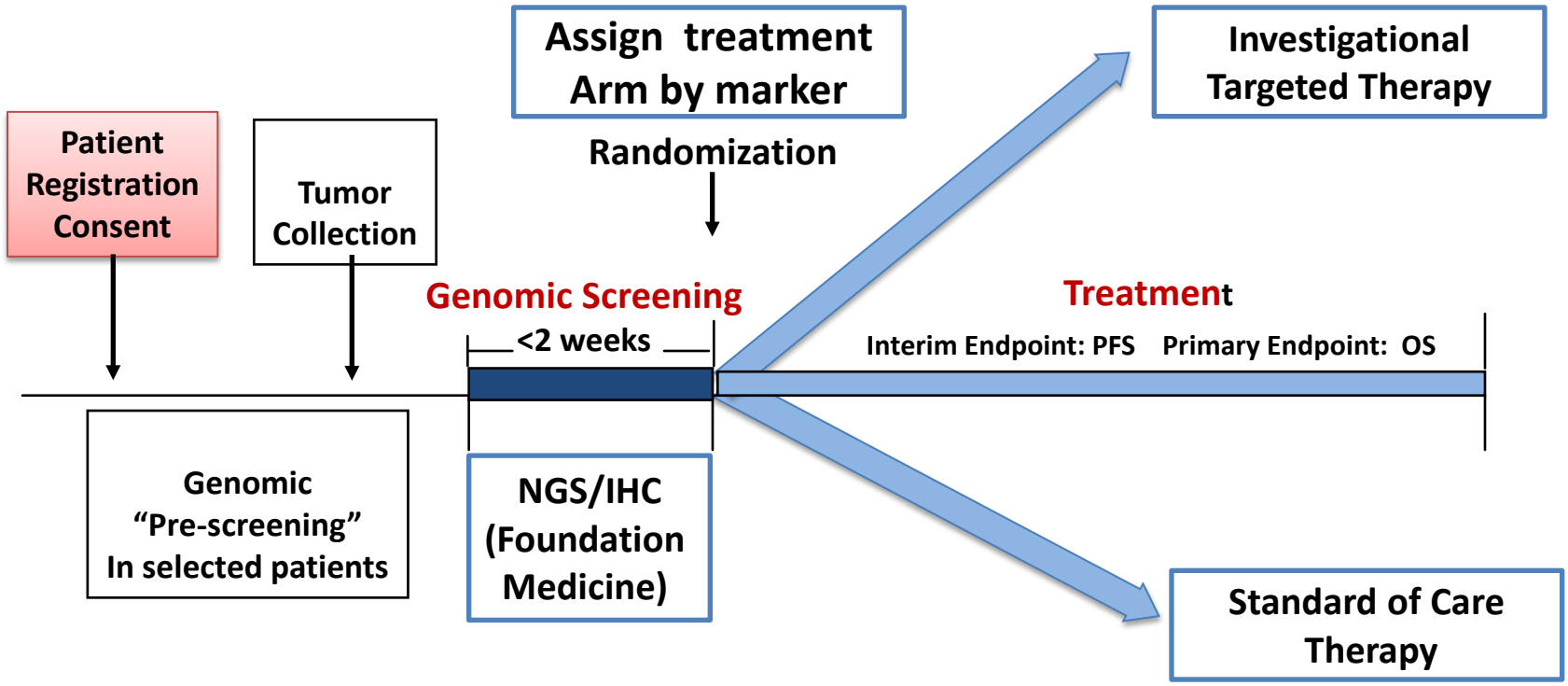
Protocol Details – Trial Design

Trial Category	ALCHEMIST SCREEN Component A151216	ALCHEMIST - ALK E4512	ALCHEMIST – EGFR A081105
Target	Registry/Intervention with biopsy at recurrence	ALK+	EGFRmut
Prevalence	all comers	~5%	~10%
Total Sample Size	6000 – 8000	378 (5% ineligible)	430 (5% ineligible)
Primary Endpoint	N/A	Overall Survival	Overall Survival
Power	N/A	80%	85%
One-sided α	N/A	0.025	0.05
Hazard Ratio	N/A	0.67	0.67

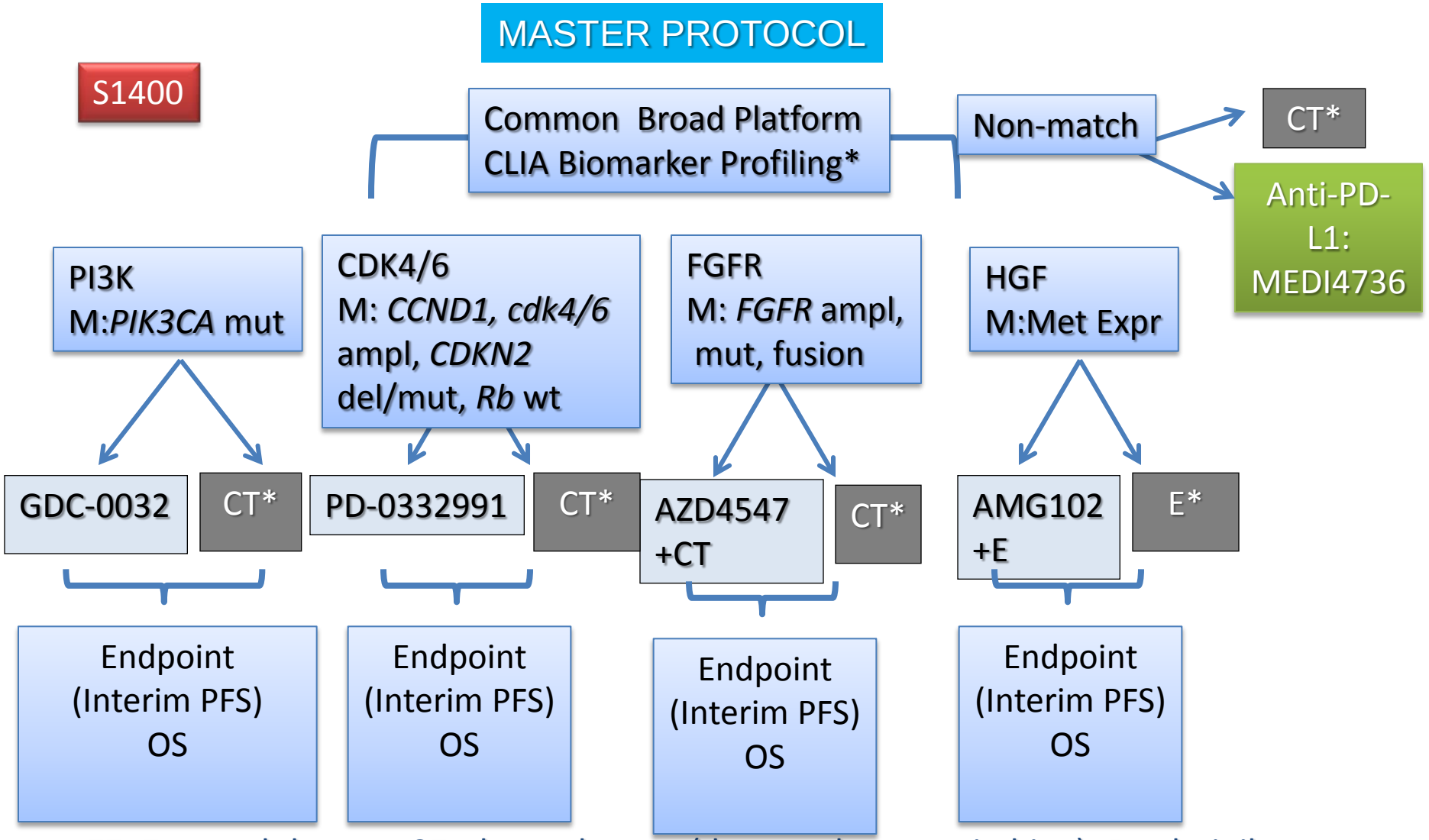
S1400: Rationale for Master Protocol Design in SCCa Lung

- Lung SCCA "orphan" group- substantial developments in therapeutics have yet to be seen versus Lung adenocarcinoma (multiple independent mutations & targets for Rx)
- Subgroup selection (genotype or phenotype-driven) refined strategy in a Multi-arm Master Protocol with improved operational efficiency: homogeneous patient populations & consistency in eligibility from arm to arm. Phase II-III design: rapid drug/biomarker testing for detection of "large effects"
- Grouping multiple studies: reduces overall screen failure rate , multi-target screening by NGS platform: sufficient "hit rate" uninterrupted accrual.
- Bring safe and effective drugs to patients faster, ineffective drugs are replaced by new improved candidates.
- Designed to allow FDA approval of new therapeutics.

MASTER PROTOCOL



- Organizers: FOCR,NCI-TMSC, FDA, FNIH
- Participants: Entire North American Lung Intergroup (SWOG, Alliance, ECOG-Acrin, NRG, NCI-Canada)
- Screening: 500-1,000 patients/year
- With 4-6 arms open simultaneously, "hit" rate ~70% in matching a patient with a drug/biomarker arm.



TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

*Archival FFPE tumor, fresh CNB if needed

Target/M: Drug target and biomarker

M-PACT: Molecular Profiling based Assignment of Cancer Therapeutics

Pilot Trial to Assess the Utility of Genetic Sequencing to Determine Therapy and Improve Patient Outcome in Early Phase Trials Independent of Tumor Histology

Objective

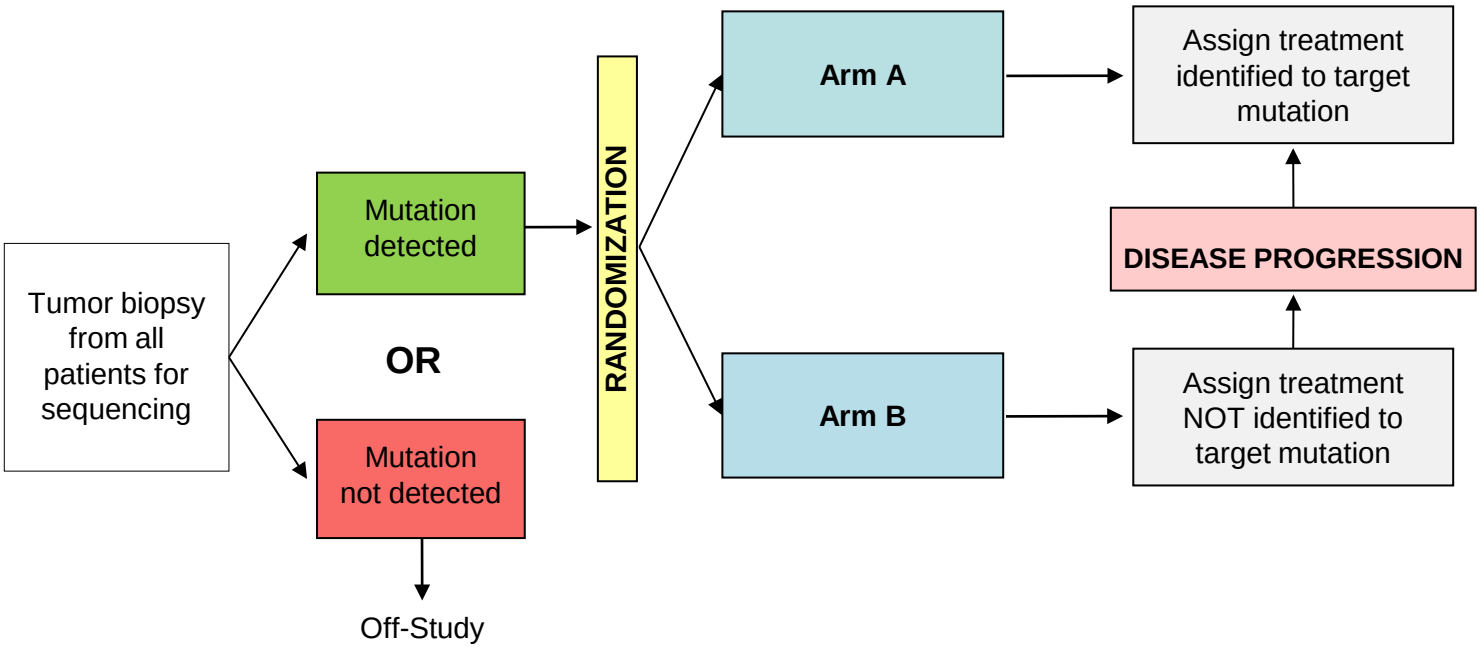
- Assess whether the response rate (CR+PR) and/or 4-month PFS is improved following treatment with agents chosen based on the presence of specific mutations in patient tumors.
  - Only patients with pre-defined mutations of interest will be eligible
  - Study treatments, regardless of cohort, will be chosen from the list of regimens defined in the protocol
  - Arm A: Receive treatment based on an study agent prospectively identified to work on that mutation/pathway
  - Arm B: Receive treatment with one of the study agents in the complementary set (identified to not work on one of the detected mutations/pathways)

Patient Population

- Patients with refractory solid tumors that have progressed on at least one line of standard therapy or for which no standard treatment is available that has been shown to improve survival.
- Adequate organ function (AST/ALT<3xULN, Bil < 1.5 xULN, S. Cr < 1.5 x ULN, platelets > 100K, ANC> 1500)
- Study regimens: As long as the same set of protocols are offered to a given set of patients, the number and actual treatments regimens can vary over time

Mutations in DNA repair pathways	Veliparib+ Temozolomide MK1775 + carboplatin
Mutations in the PI3K pathway; loss of PTEN, Akt amplification	mTOR inhibitor -Everolimus
Mutations in the RAS pathway	GSK 1120212 (MEK inhibitor)

NCI's M-PACT Clinical Trial: Study Design



- Fresh tumor biopsy on-study and at progression
- Primary endpoint response (CR + PR) and 4-month PFS improved for agents chosen on the basis of specific mutations
- Crossover from Arm B (non-mutation–directed) to Arm A (mutation-directed) treatment at progression
- Trial open across NCI's Phase I/II network (>30 NCI-designated Cancer Centers)
- Accrual expected to begin Q1-2014

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NCI-Supported Genomic Clinical Trials

Extra Slides

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ALCHEMIST TRIAL – SCREENING COMPONENT

Eligibility:

NSCLC, non-squamous

Resectable

Clinical TNM Stage for Pre-Op Option

~ OR ~

Pathologic TNM Stage for Post-Op Option

Stage 1B>4 cm, Stage IIA - IIIA

PS 0-1; Age ≥ 18

Adequate organ function

Adequate tissue for central EGFR & ALK genotyping must be available

Not known to be EGFR & ALK neg, *or* KRAS pos, on local testing

Willing to answer epidemiology questionnaire and donate de-identified data, tissue, & blood for research

If only slides are available in post-op option, only genotyping for EGFR & ALK will be done for possible assessment for adjuvant trials if positive, otherwise patient is off-study (no CCG research component)

PRE-OP (Intra-OP)

FFPE Block

Epi Questionnaire

Blood

If patient is not resectable and/or pTNM does not fit eligibility criteria, the patient is off-study

POST-OP

FFPE Block

Epi Questionnaire

Blood

OR

Slides for genotyping

Scrolls for genomics

Epi Questionnaire

Blood

Blood

Blood Sent Directly to BCR

For DNA germline analysis on patients associated with genomic research

Tissue to BCR from RGI or site

Genomic Research:

Deep sequencing; whole exon sequencing, etc.

Blocks & Slides Sent to RGI

Quality control and CLIA testing for EGFR & ALK

Scrolls and remaining tumor blocks sent to BCR

Patients whose tumors cannot be evaluated by the CLIA Central Lab for EGFR & ALK (test failures) would go off-study

If EGFR or ALK pos with CLIA Central Lab or Local Lab Testing*

If EGFR & ALK neg with CLIA Central Lab Testing

Recurrence biopsy sent to BCR

Genomic Research: comparison to baseline specimen

Assessment for Adjuvant Tx Trials

If EGFR or ALK pos but not able to go on adjuvant tx trial

Follow to recurrence or for 5-years (whichever 1st) with abbreviated collection of treatment data & annual F/U form

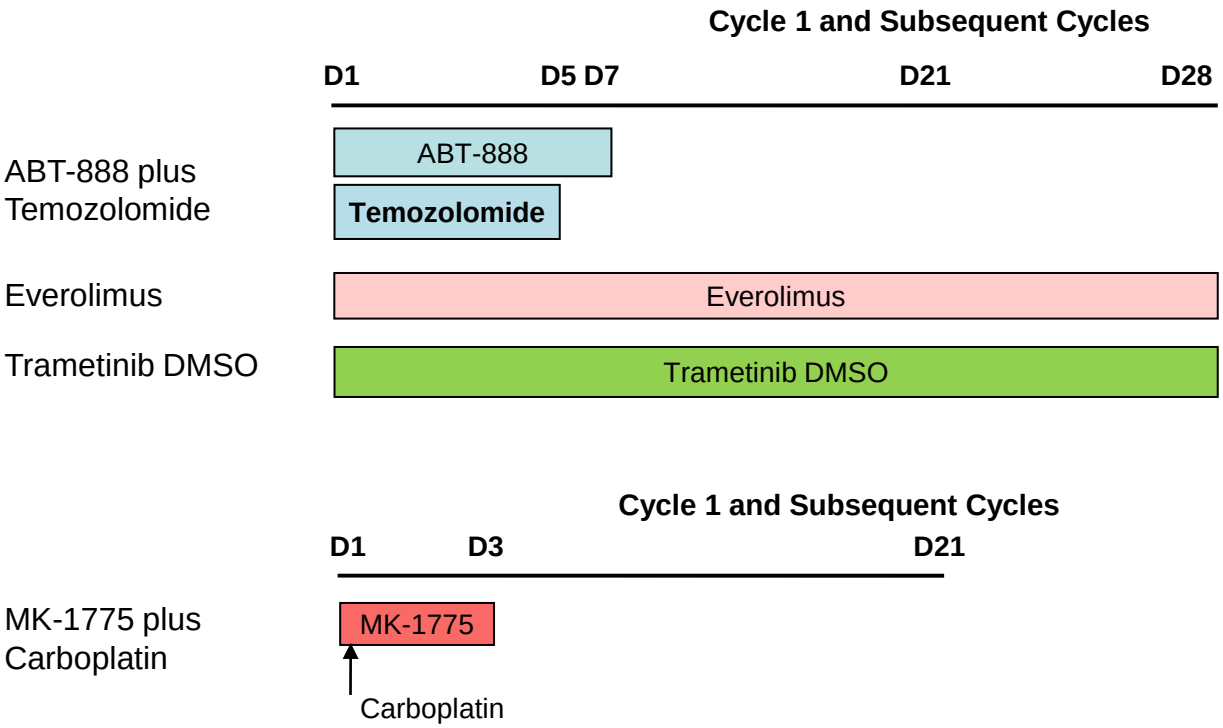
At recurrence, patients should undergo biopsy to confirm recurrence if deemed clinically appropriate by treating clinician

**Primary endpoints of the treatment trials are based on patients with EGFR or ALK pos by CLIA Central Lab; however, those pos at Local Lab but neg at Central Lab may still be randomized and followed as an exploratory subset*

Proposed initial agents

Target	Biomarker	Agent	Description/Background
PI3K	*PIK3CA* mut	GDC-0032	Small molecule PI3-kinase alpha inhibitor, increased activity in *PIK3CA mut+,* Phase I
CDK4/6	*CCND1, cdk4/6* ampl, *CDKN2* del/mut, *Rb* wt	PD-0332991	Orally active, highly selective inhibitor of CDK4 and CDK6 kinases, Ph II in NSCLC
FGFR	*FGFR* ampl, mut, fusion	AZD4547 + Docetaxel	Selective FGFR 1, 2, 3 inhibitor, phase I, Phase II NSCLC, FGFR FISH
HGF	MET Expression	AMG102 + Erlotinib	Neutralizing Ab against HGF/SF, phase III gastric Ca, MET IHC assay
PDL-1	None-"Non-match arm"	*MEDI4736*	Anti-PDL1 monoclonal antibody, phase I

13-C-0105 MPACT Clinical Trial



Patients with specified mutations of interest will be assigned to receive **<u>one</u>** of the following study drugs or drug combinations at the assigned dose. Cycle length is +/- 1 day for scheduling:

- **ABT-888** 40 mg orally BID qd days 1-7 plus **temozolomide** 150 mg/m^2 orally qd days 1-5 (no food restrictions) in 28-day cycles
- **Everolimus** 10 mg orally each day (no food restrictions) in 28-day cycles
- **Trametinib DMSO:** 2 mg orally each day either one hour before or two hours after a meal in 28-day cycles
- **MK-1775** 225 mg orally BID for 5 doses either at least two hours before or two hours after a meal plus **carboplatin** (AUC 5) IV on day 1 every 3 weeks (21-day cycle)