Biostatistics / Study design
- New study designs -

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But Bouvard was tired of medicine:

"The springs of life are hidden from us, the ailments too numerous, the remedies problematical."

Gustave Flaubert: Bouvard and Pécuchet, A Tragi-comic Novel of Bourgeois Life
chapter III, p. 92, Paris, 1881

WCLC, September 6-9, 2015 in Denver

MASTER PROTOCOL

ED07.03 Lung Master Protocol in Squamous Cell Lung Cancer (Lung-MAP, S1400)

David R. Gandara et al. p.S80

MTE02.01 / MTE02.02 Patients, Investigators and Pharmaceuticals Working Together to Accelerate Research and Access: The Lung Cancer Master Protocol (Lung-MAP) Clinical Trial

Vassiliki Papadimitrakopoulou et al. p.S141 and Kim Norris et al. p.141/S142

UMBRELLA:

PLEN03.04 Personalized Medicine; *Jordi Remon and Jean-Charles Soria, p.S69/S70*

MS28.02 Master Protocols; *Shakun Malik p.S139/S140*

BASKET:

MS28.04 Drug Development and Drug Approval; *Richard Gaynor p.S139/S140*

MTE22.01 Diagnosis and Treatment of MPM (Malignant pleural mesothelioma): Overview; *Arnaud Scherpereel p.S154*

GR03.05 Treatment of Thymic Malignancies - Targeted Agents; *Jordi Remon-Masip and Benjamin Besse p.S165/S166*

J Thoracic Oncol 2015;10(9);Suppl_2_abstracts

Recent FDA approvals (2013-2015)

FDA approvals for advanced NSCLC for targeted therapies in molecular enriched populations

Drug	Tumor	Patient population	Accelerated approval	Regular approval
Nivolumab	NSCLC / IV / Progression	EGFR+ / ALK+		Oct 2015
Pembrolizumab	NSCLC / IV / Progression	PD-L1	Oct 2015	
Gefitinib	NSCLC grade IV	EGFR exon 19/21		July 2015
Nivolumab	NSCLC grade IV SCC, PD		March 2015	
Ramucirumab	NSCLC / IV / Progression	/+Docetaxel		Dec 2014
Ceritinib*	NSCLC grade IV	ALK+	April 2014	
Crizotinib	NSCLC grade IV	ALK+	Nov 2013	
Afatinib	NSCLC grade IV	EGFR exon 19/21		July 2013
Erlotinib	NSCLC grade IV	EGFR exon 19/21		May 2013

*First lung cancer drug approved under new breakthrough designation program
PD-L1=programmed death ligand 1

Main questions in drug and biomarker (co-)development in lung cancer

Opportunities for "personalized medicine"

For which patient group does the medicine show therapeutic efficacy?

For which patient group is the risk–benefit balance favorable?

Is it possible to find an abbreviated way for development of new therapies?

Can we make use of validated treatment information in other entities?

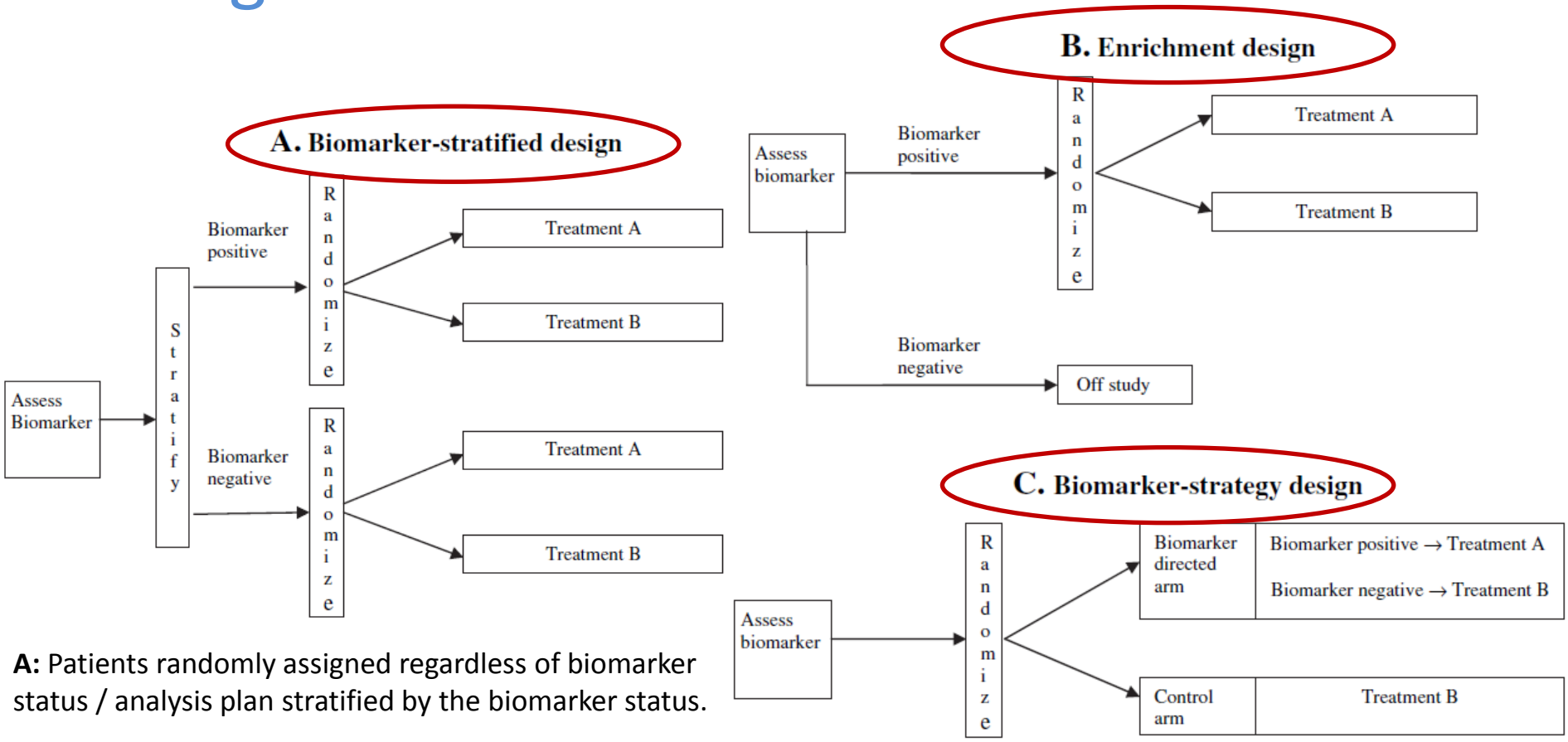
Requirements for a valid retrospective assessment of a predictive biomarker

- Data from a well-conducted randomized controlled trial
- Availability of samples on a large majority of patients to avoid selection bias
- Prospectively stated hypothesis, analysis techniques, and patient population
- Predefined and standardized assay and scoring system
- Upfront sample size and power justification

Mandrekar SJ et al. J Clin Oncol 2009;27;4027-4034

Randomized clinical trials with biomarkers: Design Issues

B: Biomarker evaluation for all patients, but random assignment restricted to patients with specific biomarker values.

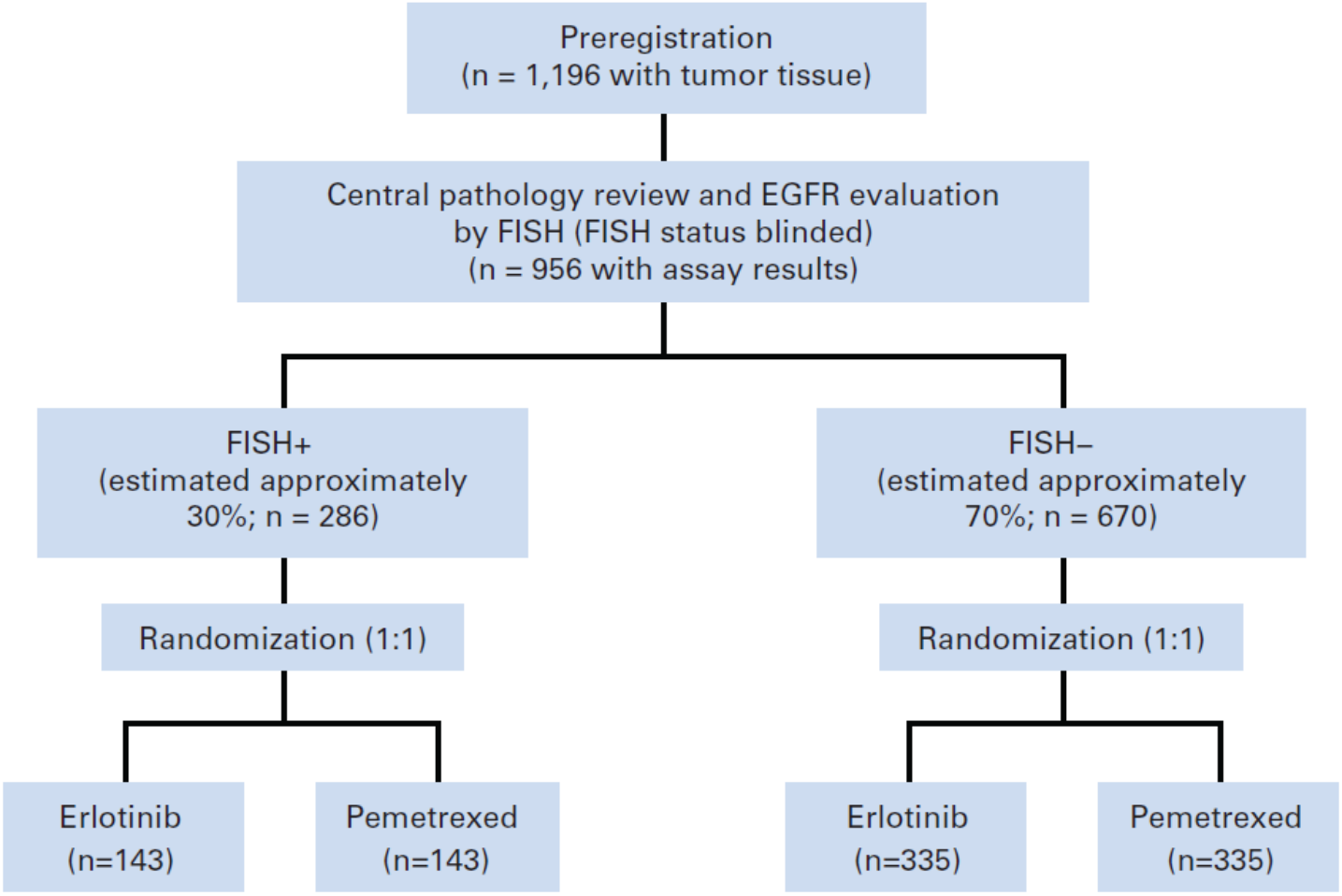


A: Patients randomly assigned regardless of biomarker status / analysis plan stratified by the biomarker status.

C: Patients randomly assigned to an experimental treatment arm that uses the biomarker to direct therapy or to a control arm that does not.

Freidlin B et al. J Natl Cancer Inst 2010;102:152–160

Marker validation for erlotinib in lung cancer: MARVEL trial design



MARVEL (Marker Validation for Erlotinib in Lung Cancer) trial design.

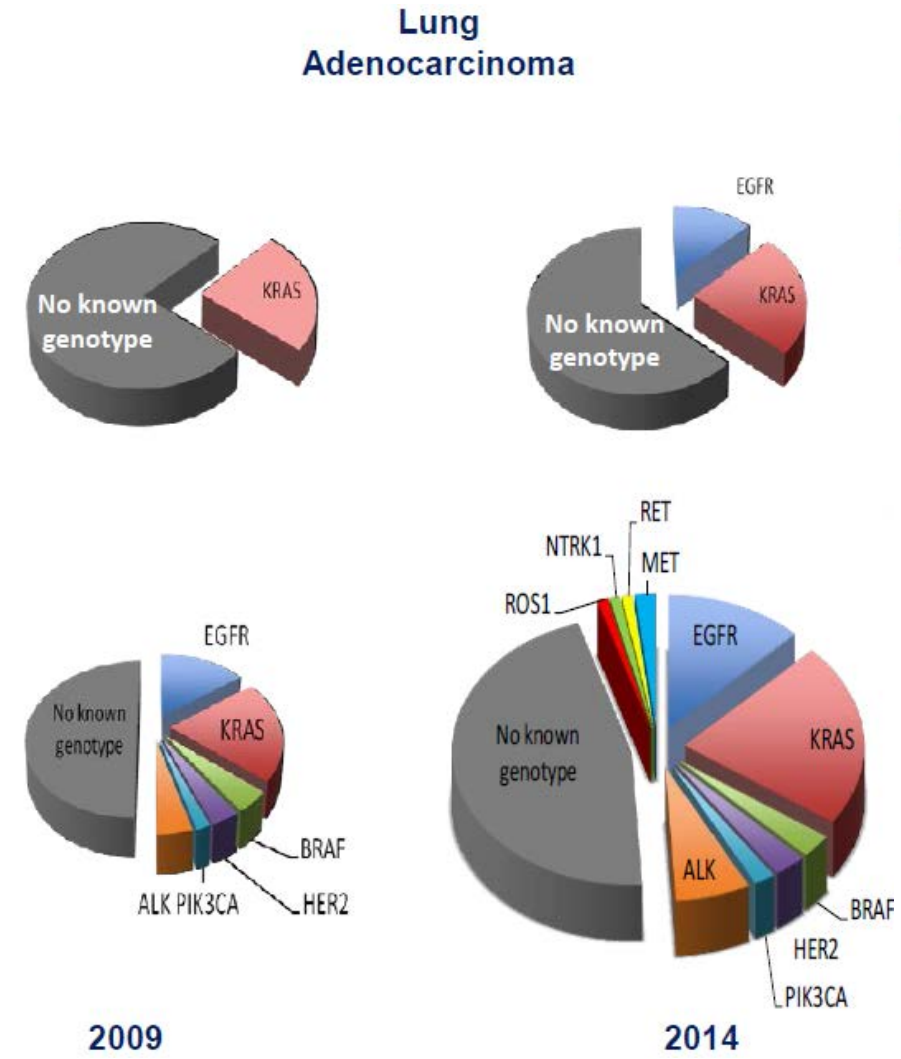
Each cycle of treatment is 21 days.

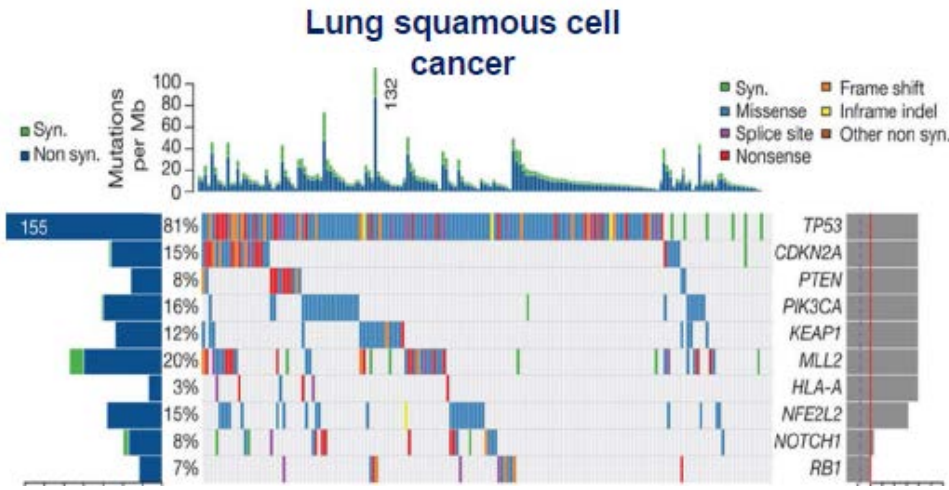
Stratification factors: ECOG performance status, gender, smoking status, histology, best response to prior chemotherapy.

EGFR, epidermal growth factor receptor; FISH, fluorescent in situ hybridization.

Mandrekar SJ et al. J Clin Oncol 2009;27:4027-4034; Freidlin B et al. J Natl Cancer Inst 2010;102:152–160

Identification of genomic alterations for NSCLC





Herbst RS; Re-thinking clinical trial designs for NSCLC, Yale Univ. , Nov 10, 2014

Umbrella or basket?

Umbrella:

Looking at a single type of cancer and branch treatment

Test the impact of different drugs on different mutations in a single type of cancer:

- BATTLE
- I-SPY2
- SWOG Squamous Lung Master

Basket:

Putting all your cancer types into one basket

Test the effect of drug(s) on a single mutation in a variety of cancer types:

- Imatinib Basket
- BRAF+
- NCI MATCH

Herbst RS; Re-thinking clinical trial designs for NSCLC, Yale Univ. , Nov 10, 2014
Gandara D et al. J Thoracic Oncol 2015;10(9);S80;Suppl_2_abstract ED07.03

The MATRIX umbrella trial for NSCLC

- Matrix NSCLC study: Dividing patients within a single cancer type by the genetic makeup of their tumor and testing multiple treatments in parallel

- Design is modular and flexible: Arms can be moved in and out of the study according to patient results and when new drugs become available

- Flexibility and the great variety of drugs tested at the same time should mean that as many patient groups as possible have their optimum treatment options identified

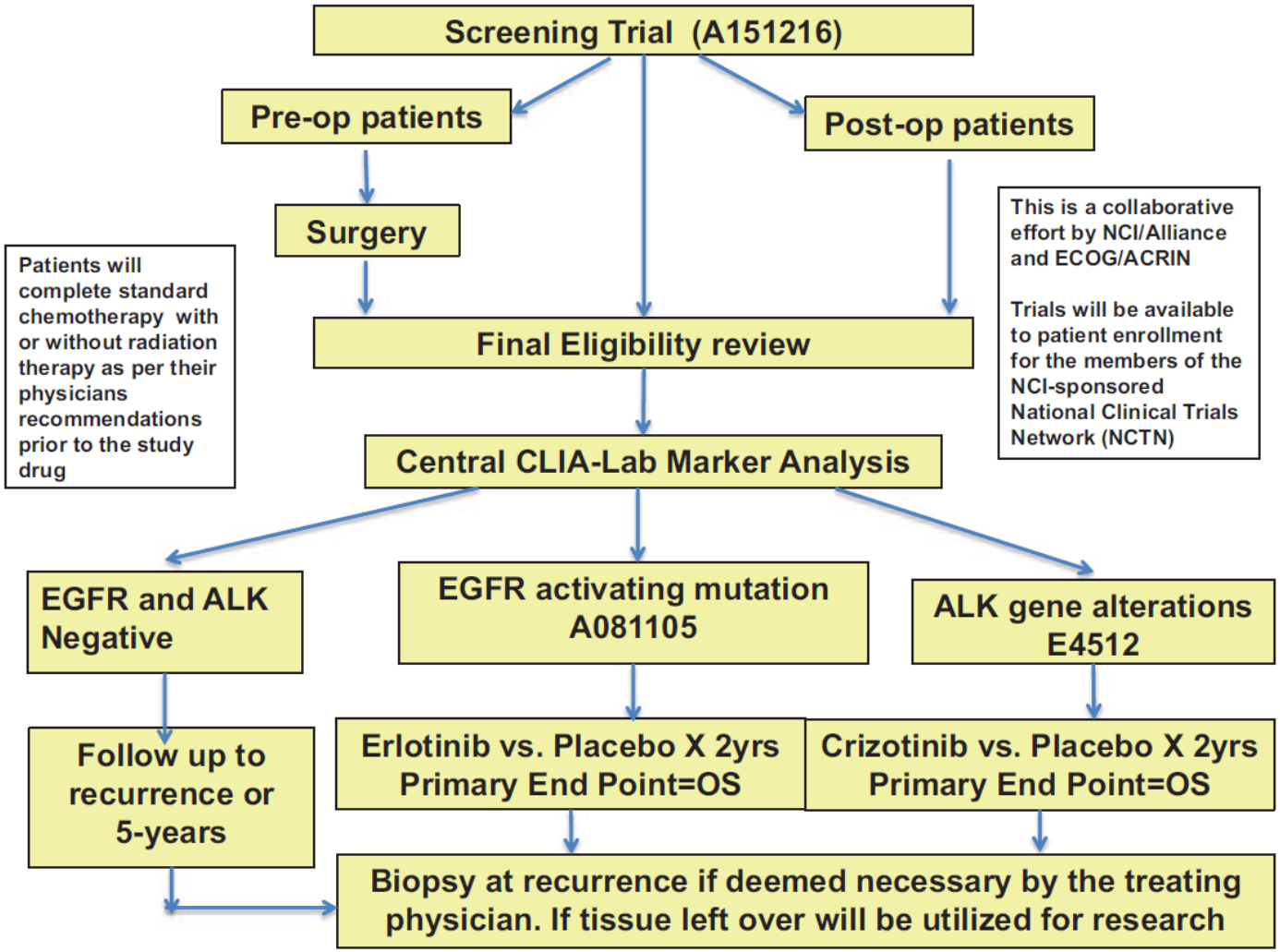
Co-development of drug and biomarker: The ALCHEMIST trial

- Enrolls patients with resectable (stage IB ≥ 4 cm, II and IIIA) adenocarcinoma of the lung, with OS as the primary end point

- In an umbrella screening protocol A151216, patients' tumors will be ***screened for EGFR mutations***
- If genetic alterations are detected in their tumors, these patients will be eligible for ***separate adjuvant studies***
- In order to enroll 410 patients in two arms of erlotinib versus placebo and 300 in crizotinib versus Placebo, it is estimated that about 6000 to 8000 patients will be needed to enroll in screening protocol.

Malik SM et al. *J Thorac Oncol.* 2014;9: 1443–1448

The ALCHEMIST trial



ALCHEMIST study schema

ALCHEMIST— A151216, screening trial;

ALCHEMIST—EGFR A081105, erlotinib treatment arm;

ALCHEMIST—ALK E4512, crizotinib treatment arm.

Malik SM et al. *J Thorac Oncol.* 2014;9: 1443–1448

Design: Main traditional obstacles for the approval of oncologic therapeutic agents

- Targeted therapies may address only a *rare-biomarker* defined group of patients;
- Long processes from initial drug discovery to clinical implementation;
- Difficulties in recruitment for these clinical trials;
- High number of screen failures;
- Overall low rate of enrollment in clinical trials.

Papadimitrakopoulou V et al. J Thoracic Oncol 2015;10(9);S141;Suppl_2_abstract MTE02.01

Lung-MAP: The master protocol

- **Lung-MAP:**
  - **S1400 Biomarker-Targeted Second-Line Therapy in Treating Patients With Recurrent Stage IIIB-IV Squamous Cell Lung Cancer**
- Establish Nat. Clinical Trials Network (NCTN) mechanism for genomic screening of large, homogeneous cancer populations
- Assign and accrue simultaneously to a *multi-sub-study "Master Protocol"*
  - comparing new targeted therapies to standard of care,
  - based on designated therapeutic biomarker-drug combinations

Southwest Oncology Group , National Cancer Institute (NCI) NCT02154490

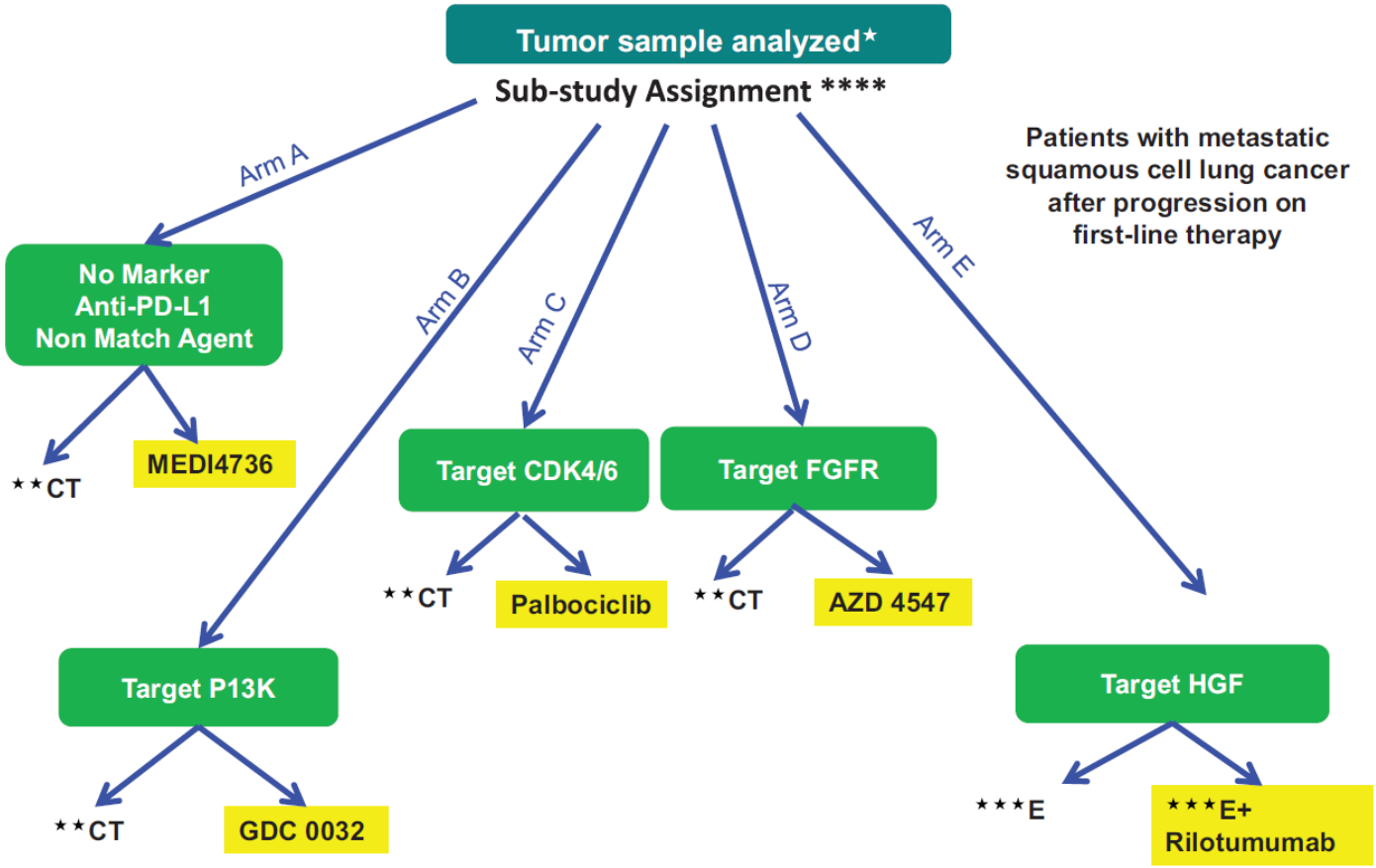
Lung-MAP: Major goals

- Improved genomic screening for clinical trial entry
- Improved time lines for drug-biomarker testing
- Allowing for
  - Inclusion of the maximum numbers of otherwise ***eligible*** patients in comparison with currently employed "single screen trial" approaches.
- Ultimate goal is to identify and approve quickly

Safe and effective regimens (monotherapy or combinations) based on (matched) predictive biomarker-targeted drug pairs.

Southwest Oncology Group , National Cancer Institute (NCI) NCT02154490

The Lung-MAP Trial (S1400)



Phase II/III biomarker-driven master protocol for second-line therapy of squamous cell lung cancer (Lung-MAP Trial).

*Archival formalin-fixed paraffinembedded (FFPE) tumor, fresh core needle biopsy if needed.

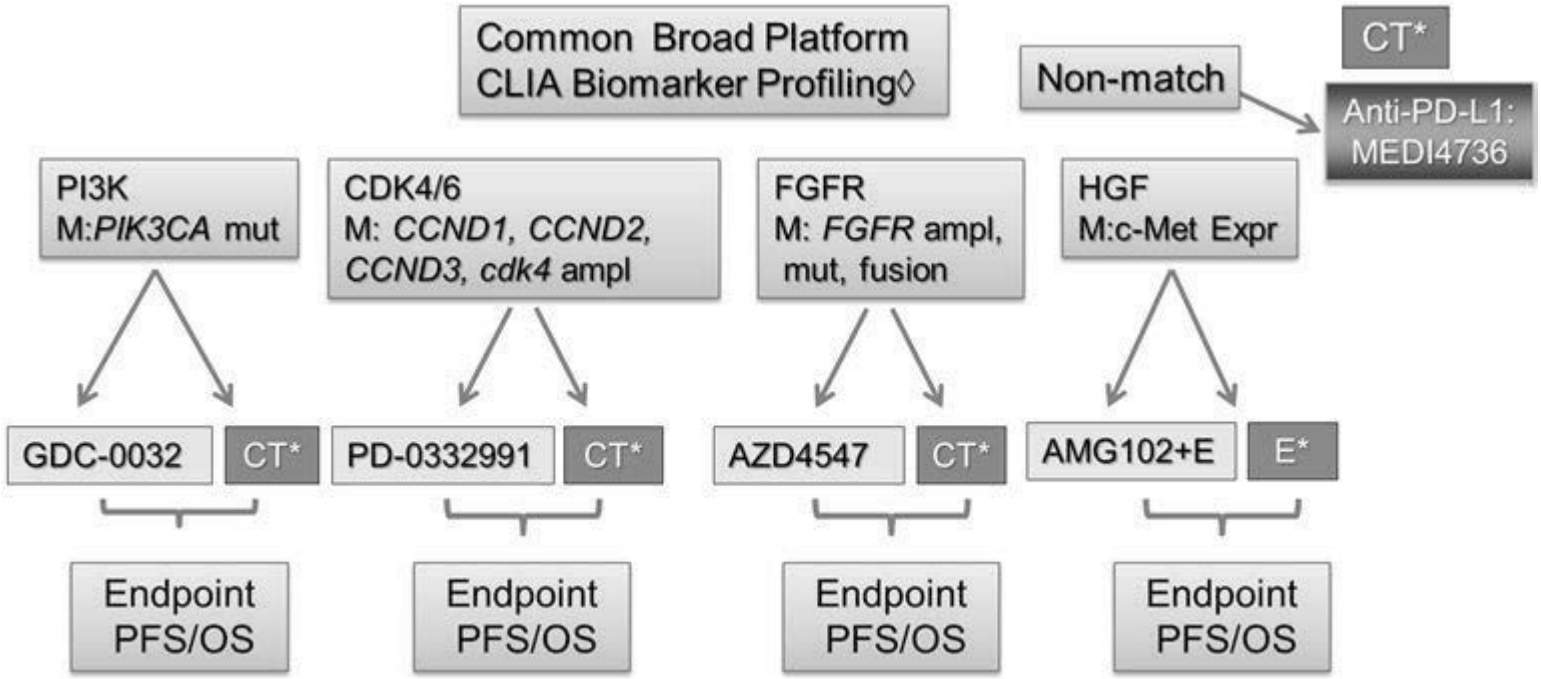
**CT = chemotherapy (docetaxel) control arm.

***E = erlotinib control arm.

****Substudy assignment will be determined based on randomization for patients eligible for multiple substudies.

Southwest Oncology Group , National Cancer Institute (NCI) NCT02154490

The Lung-MAP Trial: Original study design



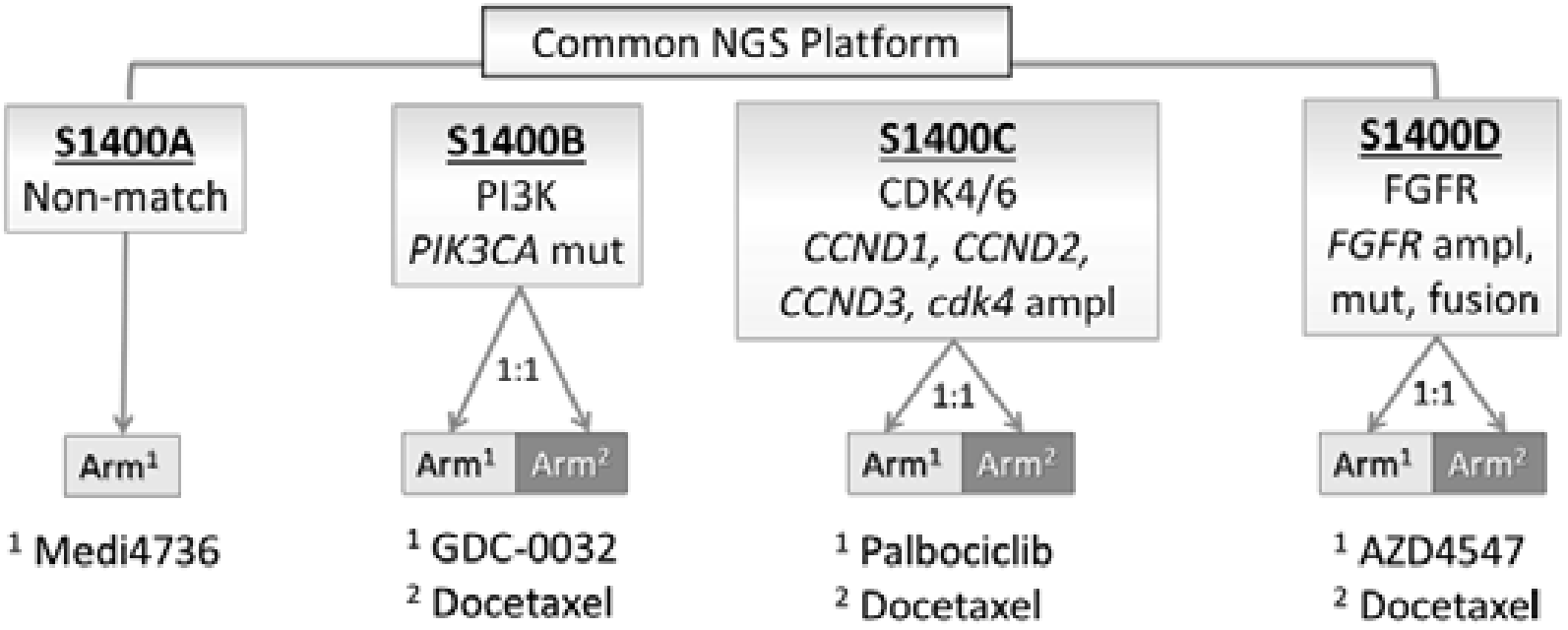
Papadimitrakopoulou V et al. J Thoracic Oncol 2015;10(9);S141;Suppl_2_abstract MTE02.01

The Lung-MAP Trial: Alterations

- Modular study design allows for flexibility
  - To adapt to the approval of a new drug (nivolumab)
  - To halt in further development of AMG102 (rilotumumab)
- With discontinuation of the corresponding sub-study by implementing timely modifications
- Which include the following:
  - Eligibility has changed from exclusively second line therapy to second-or more line therapy
  - Pre-screening, while patient receive first-line therapy has been added to boost accrual
  - The unmatched arm changed to a single (not randomized) arm study with the anti-PD-L1 agent MEDI-4736.

Papadimitrakopoulou V et al. J Thoracic Oncol 2015;10(9);S141;Suppl_2_abstract MTE02.01

The Lung-MAP Trial: Renewed study design



Papadimitrakopoulou V et al. J Thoracic Oncol 2015;10(9);S141;Suppl_2_abstract MTE02.01

Putting all your cancer types in one basket

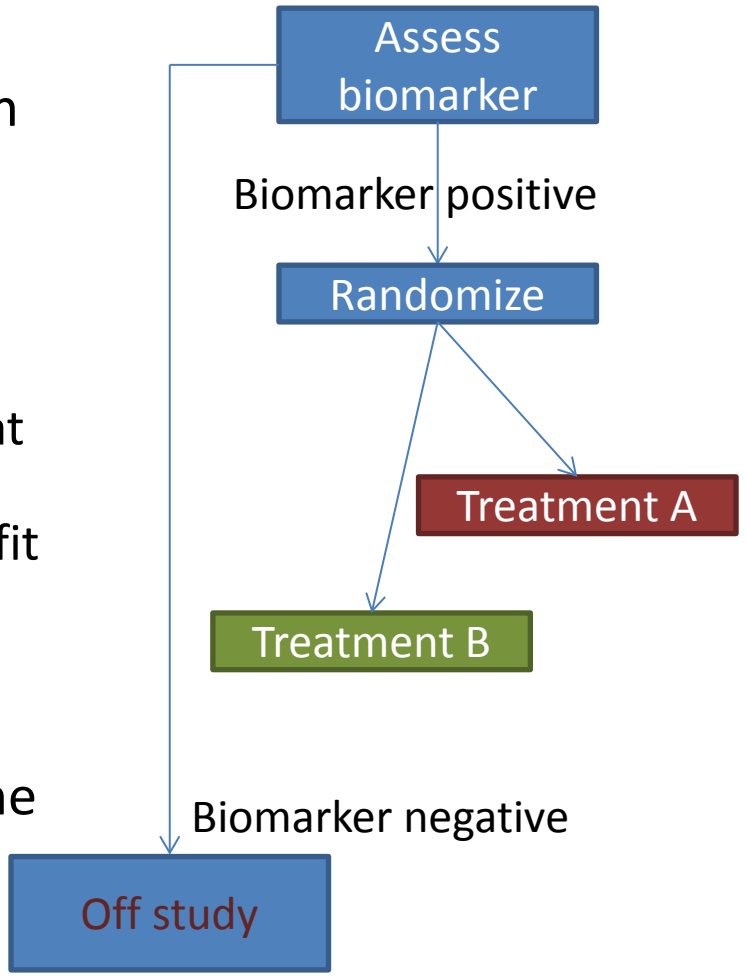
- "Classical" clinical trial design in one cancer type has a high attrition rate *(estimated 95% of potential anticancer drugs fail during development)*
- One method is to perform a "basket" study, grouping together patients by mutation type rather than disease
- A possible key to predict subgroup response
- Enroll at least 10 to 15 subjects per cancer type, putting each cancer in its own separate study arm
  - Each arm/cancer type is analyzed separately for response, as well as the overall study population being assessed as a whole

The basket strategy: Pros and cons

- This phenotype-to-genotype is trial useful if
  - A mutation or cancer type is rare
  - Small number of evaluable "*targeted*" patients
- Studies usually include an arm for "other": patients who have the mutation of interest in a rare, or never before seen, cancer type.
- Problem: FDA approval from basket studies
  - FDA still approves agents from studies involving a ***smaller number of patients***
  - It is not likely to approve a drug based on data from only a ***few subjects***
- Studies may need to expand around one specific arm
- Possibly the need to run further follow up studies
- Currently, FDA usually approve agents based around a cancer type rather than a molecular target
- Only with solid data, there is a chance that the FDA would welcome this new trial type.

Adaptive enrichment design for clinical trials

- Patients are first evaluated for biomarker expression
- Test positive: Deemed eligible for inclusion in the study
- Test negative: Patients out of study
- Adaptive enrichment designs allow the eligibility criteria of a trial
  - To be adaptively updated during the trial at fixed interim analysis points
  - Restricting entry to patients likely to benefit from the new treatment
- Example:
  - ALK-positive lung cancer (crizotinib)
- Statistical significance test at the end of the trial *(type I error is preserved)*:
  - Fixed sample size regardless of changes in eligibility (except termination)



Simon N and Simon R *Biostatistics* 2013;**14**(4):613–625

Adaptive enrichment: Parameters to consider for choice of a design

Criteria	Design	
	Enrichment	All-Comers
Preliminary Evidence		
1. Strongly suggest benefit in marker defined subgroups.	Yes	--
2. Uncertain about benefit in overall population vs marker defined subgroups	--	Yes
Assay Reproducibility and Validity		
1. Excellent (high concordance between local and central testing; commercially available kits etc.)	Yes	--
2. Questionable	--	Yes
Turnaround Times		
1. Rapid (2-3 days; without causing delay in the start of therapy)	Yes	Yes
2. Slow to Modest (one week or more)	--	Yes (retrospective marker subgroup assessment)

Mandrekar SJ and Sargent DJ. J Thorac Oncol 2011;6(4),658–660

Conclusion / Taking home message

- Incorporating a pharmaco-dynamic biomarker requires careful consideration but can expand the capacity of clinical trials to personalize treatment decisions and enhance therapeutics development
- Umbrella (and basket) strategies can accelerate therapy development and is an information accumulating strategy
- Adaptive enrichment is more simple and in some situations promising

Hoho ! the 'brella's caught the breeze,
And Robert sails above the trees !
Above the houses, church and steeple,
and out of sight of all the people !

Heinrich Hofmann, MD, “The tale of the flying Bob”, Frankfurt, 1845

Thank you for your attention