Strategies for Integrating Predictive Biomarkers into Clinical Trial Design: A Changing Paradigm

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Disclosures

- **Research Grants: BMS, Genentech, GlaxoSmithKline, Lilly, Merck, Novartis**
- **Consultant: Ariad, AstraZeneca, Boehringer-Ingelheim, BMS, Celgene, Daiichi-Sankyo, GlaxoSmithKline, Genentech, Lilly, Merck, Novartis, Pfizer, Response Genetics, Synta**

Prognostic versus Predictive Biomarkers

Prognostic Marker

Information about disease outcome independent of treatment

Example : ***EGFR Mutation in NSCLC***
Mutation +: ***better prognosis***
Mutation - : ***worse prognosis***

Predictive Marker

Information on disease outcome related to a specific treatment

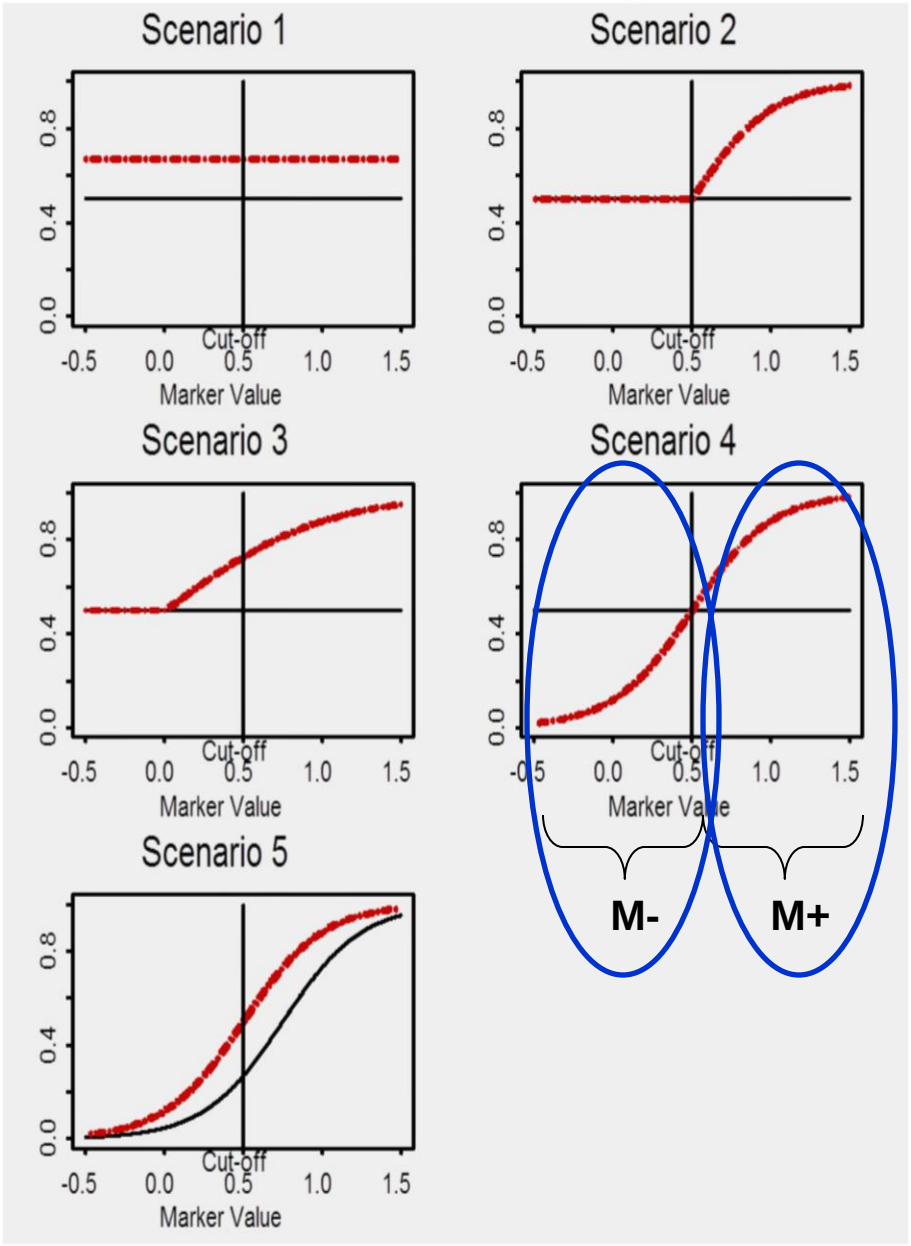
Example : ***EGFR Mutation in NSCLC***
Mutation + : ***~70% probability of response to EGFR TKI therapy***
Mutation - : ***<5% probability of response to EGFR TKI therapy***

Some biomarkers are both prognostic & predictive

Only predictive biomarkers can be used to indicate "which patients should be treated with which drug" (a Targeted Therapy)

Predictive biomarkers can also identify patients who may be harmed by "targeted therapy"

Possible Outcome Scenarios: Marker+ versus Marker-



M+ : Marker positive, Marker value > cut-point
M - : Marker negative, Marker value < cut-point

T1: Standard Therapy
T2: New (Experimental) Therapy

***Scenario 1*: biomarker is neither prognostic nor predictive**

Predictive Markers:
***Scenario 2*: T2 benefits M+ pts, but not M- pts**

***Scenario 3*: T2 benefits M+ & M- pts, but effect on M+ pts is more**

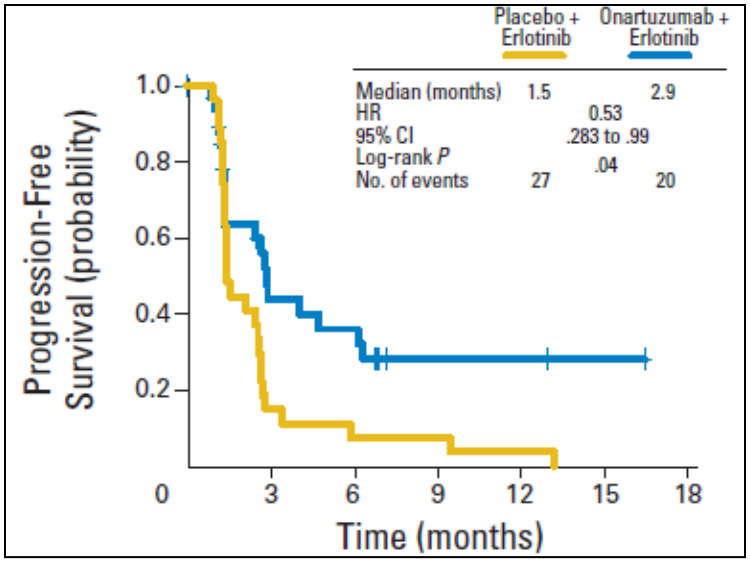
***Scenario 4*: T2 benefits M+ pts, but is harmful to M- pts (total interaction)**

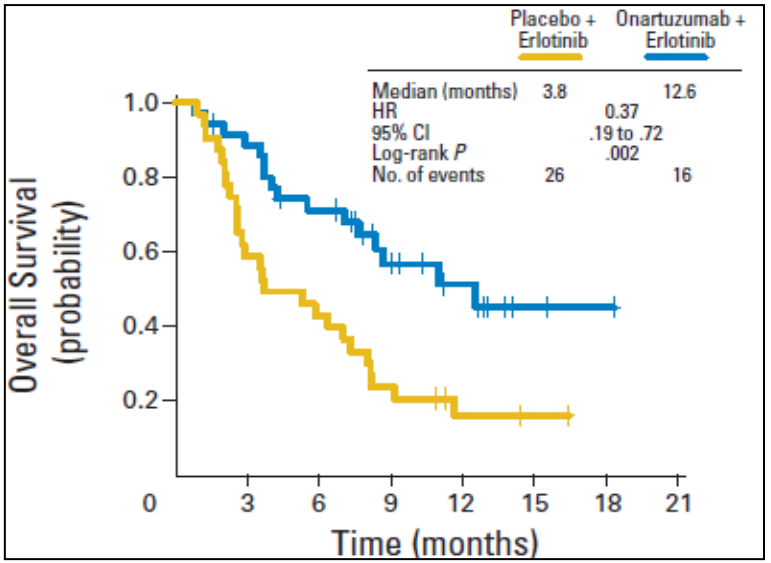
***Scenario 5*: Prognostic Marker (no predictive value)**

Hoering, Crowley et al: CCR, 2008

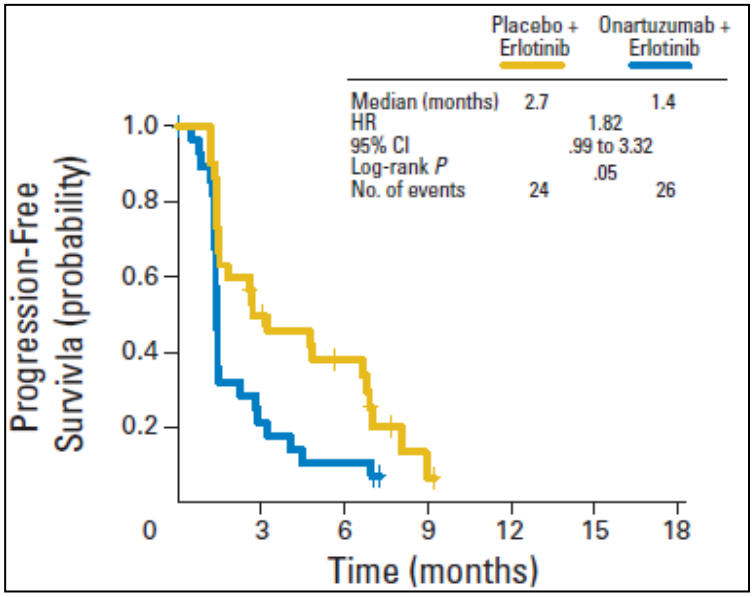
Phase II Trial of Erlotinib +/- MetMab: PFS & OS

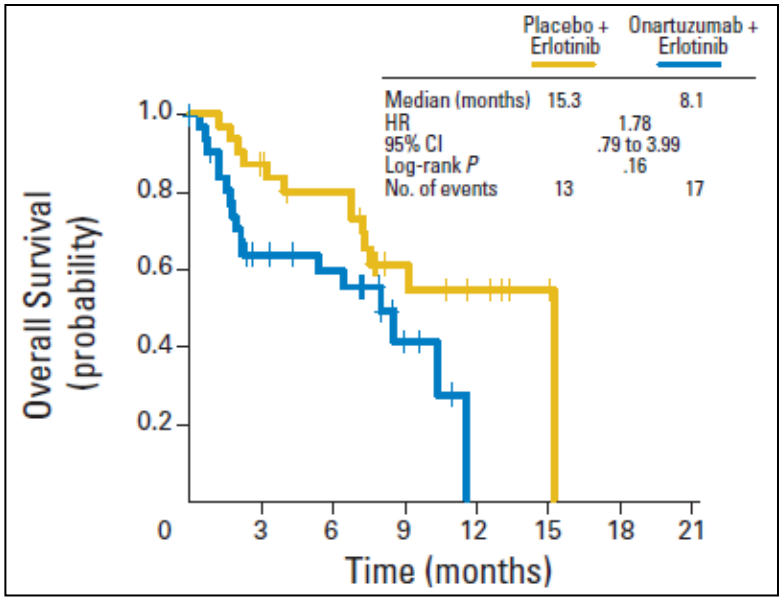
Met High





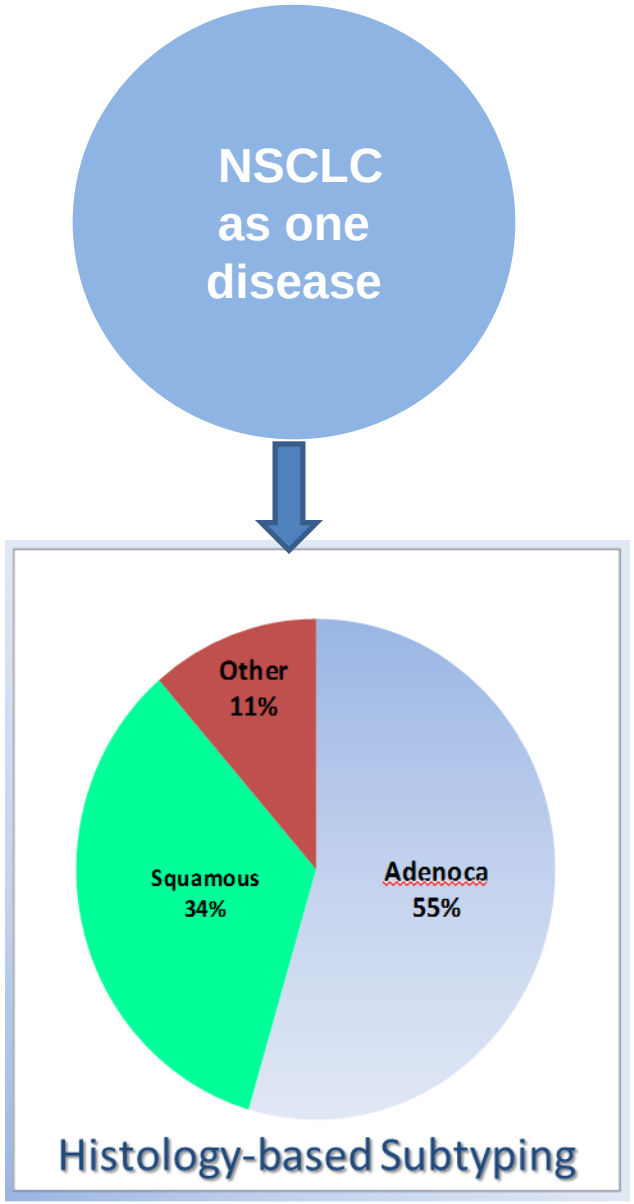
Met Low



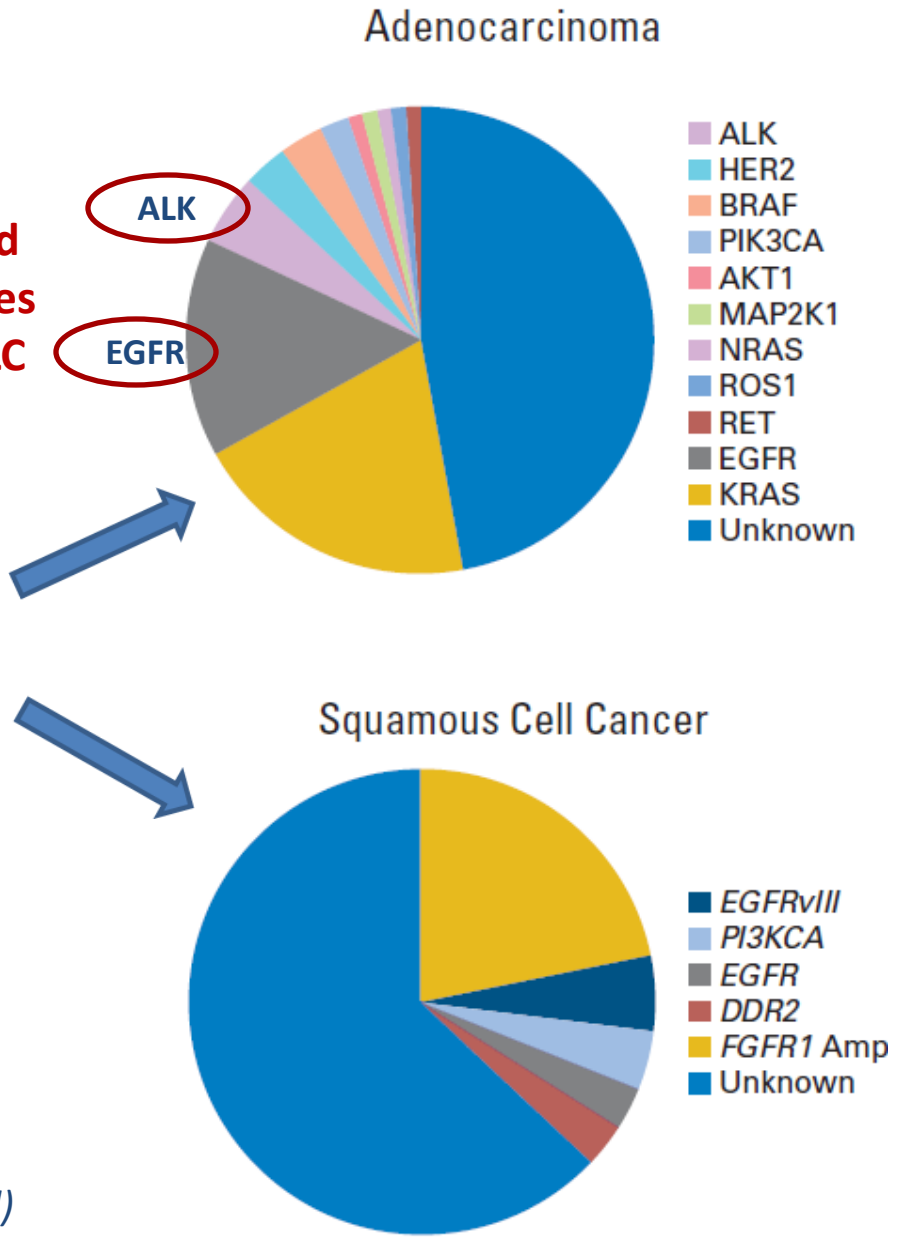


Targeted Agents can do harm in the wrong patient population

Evolution of NSCLC Subtyping from Histologic to Molecular-Based



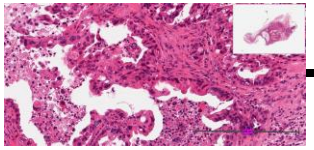
First Targeted Therapies In NSCLC



Li, Gandara et al: JCO 2013 (adapted from Pao et al)

Integration of Biomarkers into Clinical Practice: Past, Current & Future

1. Histomorphological Diagnosis:



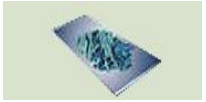
Empiric Approach (Past) (Compound-Based Therapy):
Clinical-histologic factors to select drugs for individual patients

2. Molecular Diagnosis:

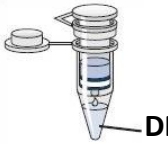
Archival FFPE tumor specimens

Archival cancer specimens

Macro- or Micro-dissection of Tumors



Extract tumor nucleic acids:



Current Approach (Target-Based Therapy V1.0):
Single gene molecular testing for decision-making in individual patients

Evolving Approach (Target-Based Therapy V2.0):
Multiplexed molecular tests with increased sensitivity & output for decision-making in individual patients

Near-Future Approach (Patient-Based Therapy):
Genomic profiling by high throughput next generation sequencing for decision-making in individual patients

Representative technologies:

Single Biomarker Tests:
- Sanger DNA Sequencing
- RT-PCR
- FISH
- IHC

Multiplex, Hot Spot Mutation Tests:
- PCR-based SNapShot
- PCR-based Mass Array SNP
- Sequenom

Initial High-Throughput Technologies:
- SNP/CNV DNA microarray
- RNA microarray

Next Generation Sequencing (NGS):
- Whole Genome or Exome capture Sequencing (DNA)
- Whole or Targeted Transcriptome Sequencing (RNA)
- Epigenetic profiling

from Li, Gandara et al: JCO , 2013

Need for Paradigm Shift in Targeted Therapy Clinical Trial Design (Presumes Biomarker Potential)

"All Comer" Phase III Design adding Targeted Therapy to Chemotherapy

- When Marker not known or not validated (analytical)
- Marker (if known) can be retrospectively assessed
- Cautionary Tale: Most Phase III "All Comer" trials in NSCLC targeted therapy fail
- May be random differences in Marker+ and Marker- proportions per arm

Gandara et al: NCI CAPR Workshop, April 2011

Classic RCT Design (Unselected): Phase III Trials of Chemotherapy +/- Targeted Agent* in 1st-line Therapy of Advanced Stage NSCLC

Target	Agent	Survival Benefit
MMPs	Prinomastat, Others	No
EGFR TKI	Gefitinib or Erlotinib	No
Farnesyl Transferase (RAS)	Lonafarnib	No
PKCα	ISIS 3521	No
RXR	Bexarotene	No
VEGFR (TKI)	Sorafenib	No
VEGF (Mab)	Bevacizumab	Yes
EGFR (Mab)	Panitumumab	No
TLR9 Agonist	PF-351	No
EGFR (Mab)	Cetuximab	Yes**
IGR1-R	Figitumumab	No
VDA	ASA-404	No

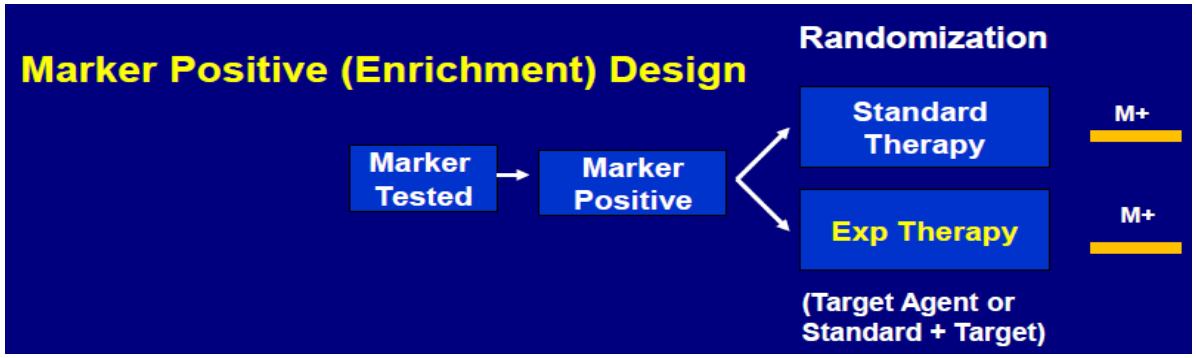
*In combination with platinum-based chemotherapy versus chemotherapy

**EGFR IHC positive

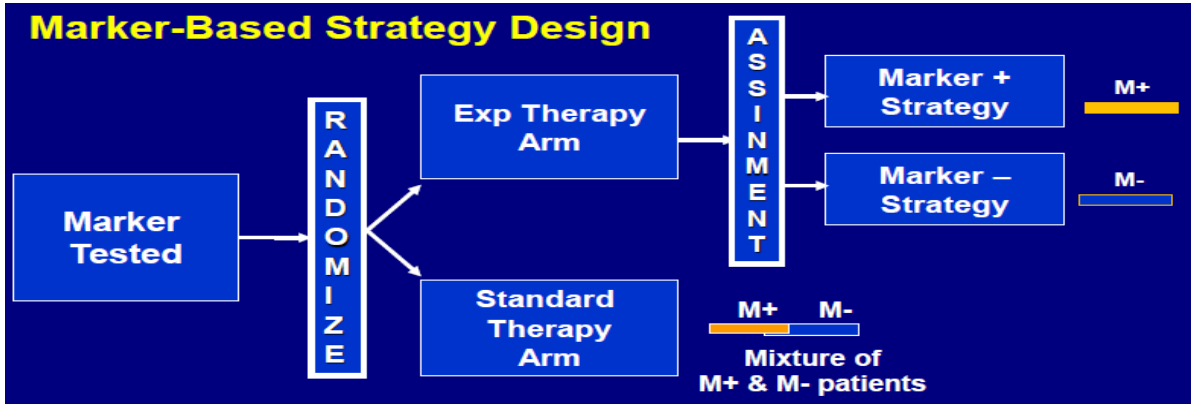
from Gandara et al: Clin Lung Cancer, 2012

Biomarker-driven Clinical Trial Designs (selected)

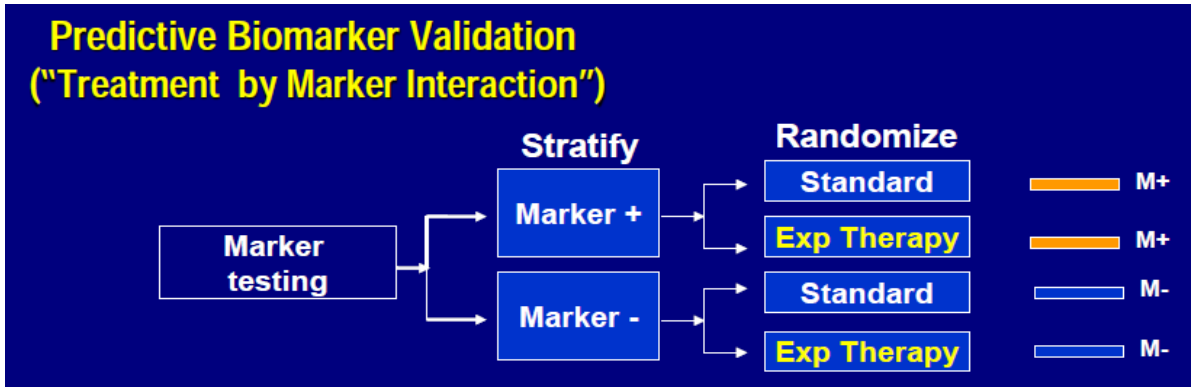
Examples:
Trastuzumab in Breast CA
EGFR TKIs in EGFR MT+ NSCLC



Example:
SLCG trial of
ERCC1-driven therapy

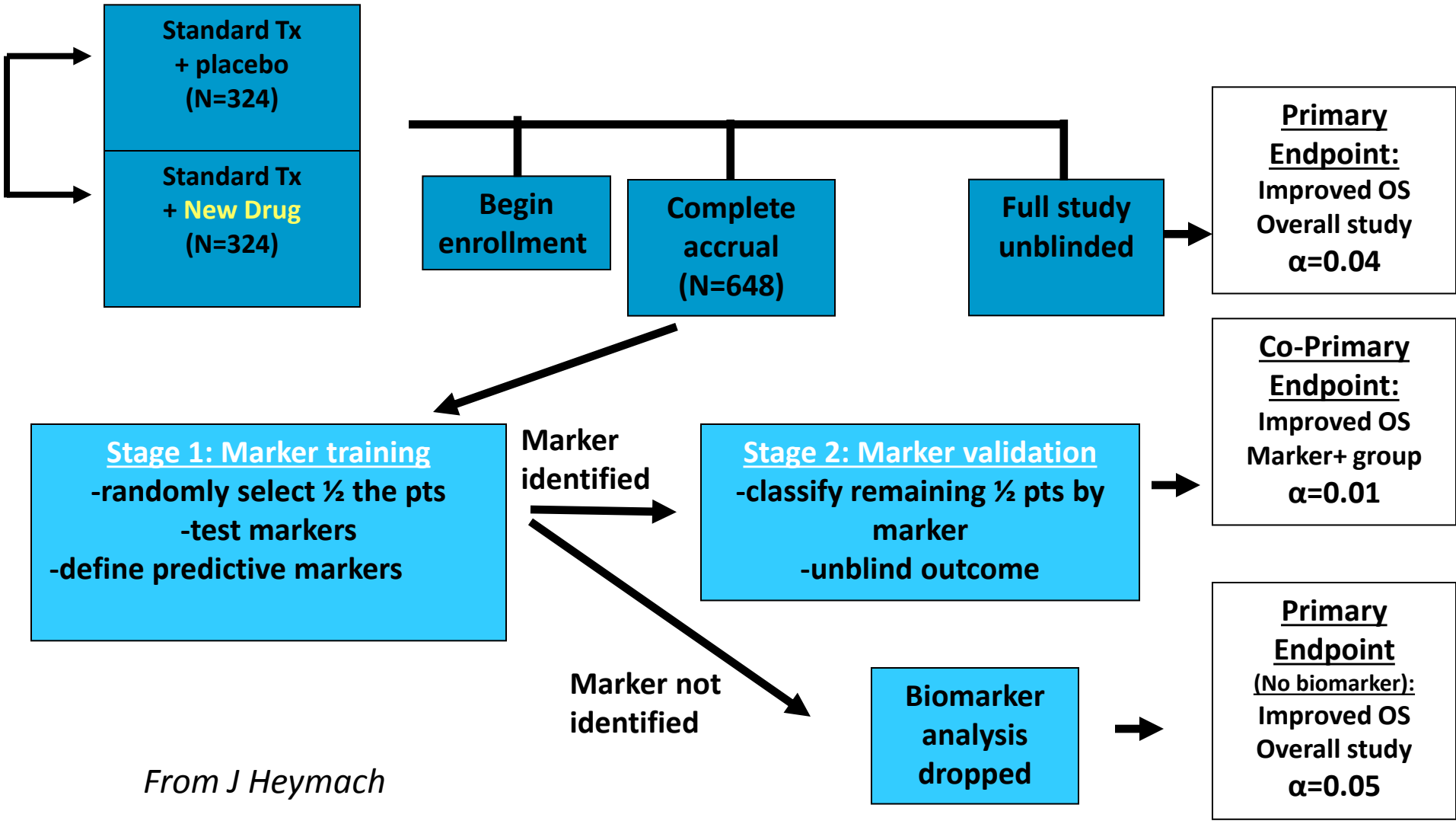


Example:
NCI-MARVEL trial



Gandara et al: NCI CAPR Workshop, April 2011

Phase III Embedded Biomarker Testing & Validation



From J Heymach

Integrated New Drug-New Biomarker Development Paradigm:

Phases of Development of a New Drug

Pre-clinical	Phase I	Phase II	Phase III	Drug Approval
	N=30	N=300	N=1600	Total Time ~90 mos (7.5 years)
~18 mo.	~18 mo.	~18 mo.	~36 mos	

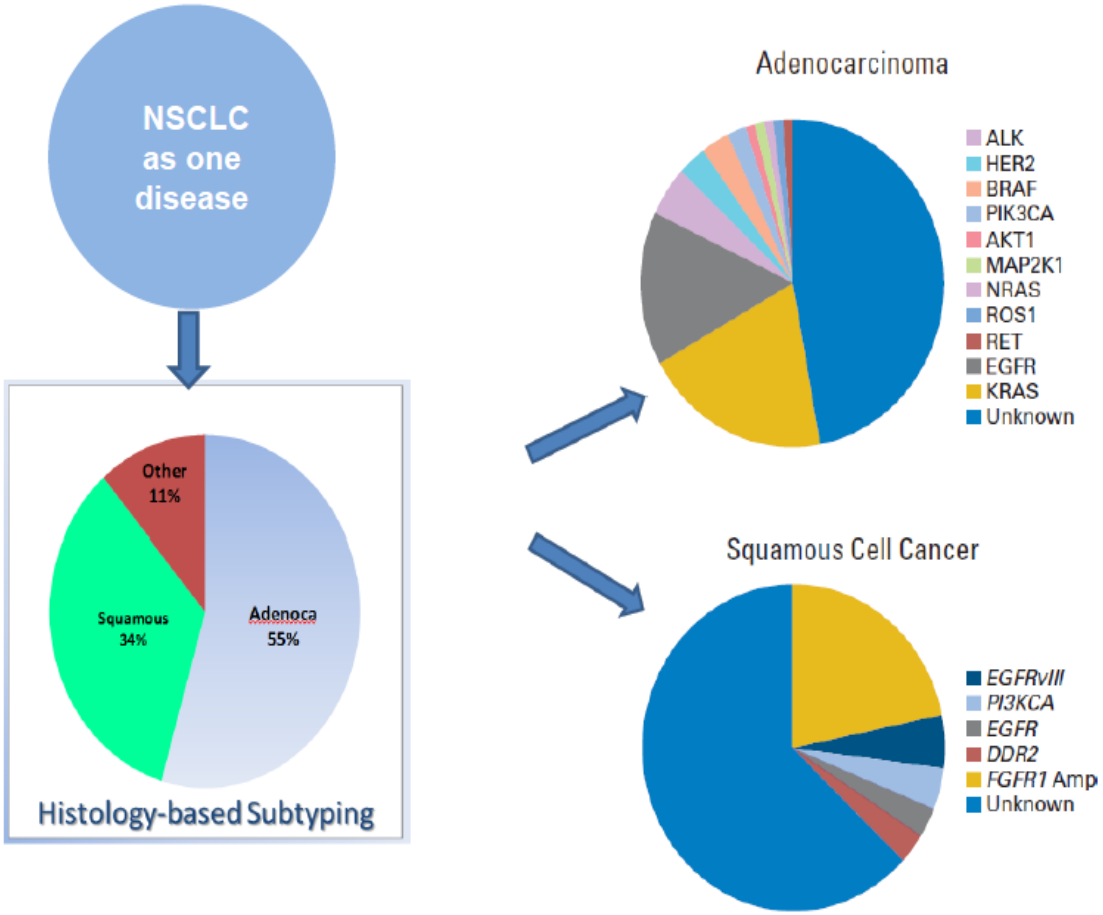
Phases of Development of New Biomarker linked to New Drug

Confirm Target	Integrate Biomarker	Biomarker Informative?	Clinical Validation	Clinical Application of Biomarker
Assay Development	Assay Performance	Assay Validation	Co-Primary Endpoint	

from Gandara et al: Clin Lung Cancer, 2012

Unmet Needs in Future NSCLC Clinical Trials when viewed as a Multitude of Genomic Subsets

Evolution of NSCLC → Histologic Subsets → Genomic Subsets



Unmet Needs in Clinical Trials:

- **How to speed drug development for uncommon-rare genotypes?**
- **How to apply broad-based genomic screening (NGS)?**
- **How to account for both inter- and intra-tumor heterogeneity in clinical trials?**
- **How to design trials to circumvent or prevent acquired resistance in oncogene-driven subsets?**

Li, Mack, Kung, Gandara: JCO 2013 (adapted from Pao et al)

"Strategies for Integrating Biomarkers into Clinical Development of New Therapies for Lung Cancer"

A Joint NCI Thoracic Malignancies Steering Committee-FDA Workshop

Bethesda MD – February 2-3, 2012

- Trial Design Challenges in the Era of Biomarker-driven Trials
  - Innovative Statistical Designs
  - Challenges for Community Oncology Practice participation
  - The Patient Perspective
- Drug & Biomarker Co-Development in Lung Cancer
  - Need for Early Co-Development
  - Need for Improved Pre-Clinical Models with clinical relevance
- Development of Future Lung Cancer Trials
  - TMSC Master Protocol Task Force in NSCLC
  - Biomarker-driven trial designs in both early stage adjuvant therapy & advanced stage NSCLC
  - Account for inter-patient tumor heterogeneity & genomic complexity of NSCLC

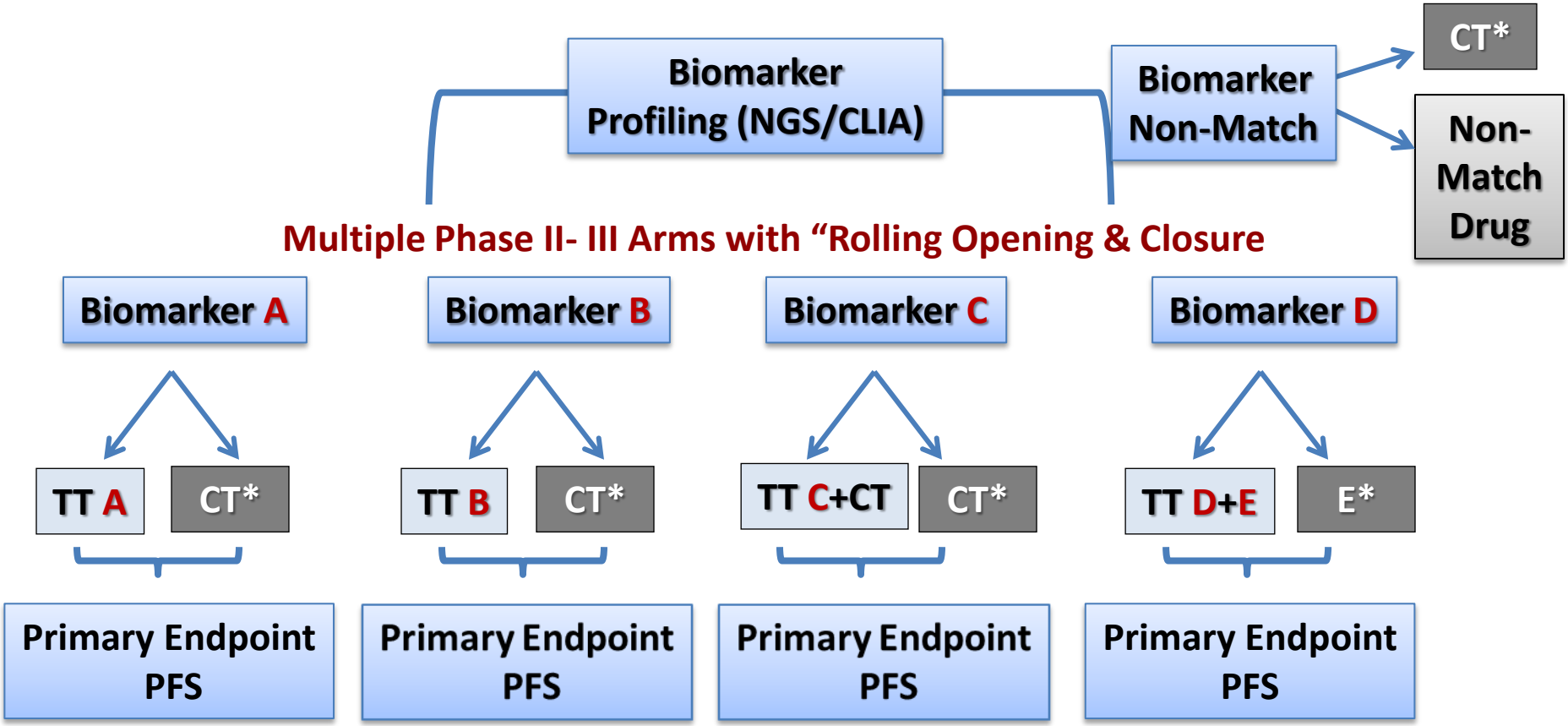
Selection of Therapeutic Targets for SCCA: Rationale for S1400 Master Lung Protocol

- SCCA repesents an unmet need
- Candidate targets are available from results of TCGA project & other studies, identified by a biomarker
- Drugs (investigational) are now available for many of these targets
- Trials can be designed to allow testing of multiple new drug-biomarker combinations at the same time ("MASTER PROTOCOL" concept)

Therapeutic targets
SCCA-TCGA 2012

Gene	Event Type	Frequency
CDKN2A	Deletion/Mutation/ Methylation	72%
PI3KCA	Mutation	16%
PTEN	Mutation/Deletion	15%
FGFR1	Amplification	15%
EGFR	Amplification	9%
PDGFRA	Amplification/Mutation	9%
CCND1	Amplification	8%
DDR2	Mutation	4%
BRAF	Mutation	4%
ERBB2	Amplification	4%
FGFR2	Mutation	3%

S1400: MASTER LUNG-1: Squamous Lung Cancer- 2nd Line Therapy



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

Project Chair: V. Papadimitrakopoulou
Steering Committee Chair: R. Herbst
SWOG Lung Chair: D. Gandara

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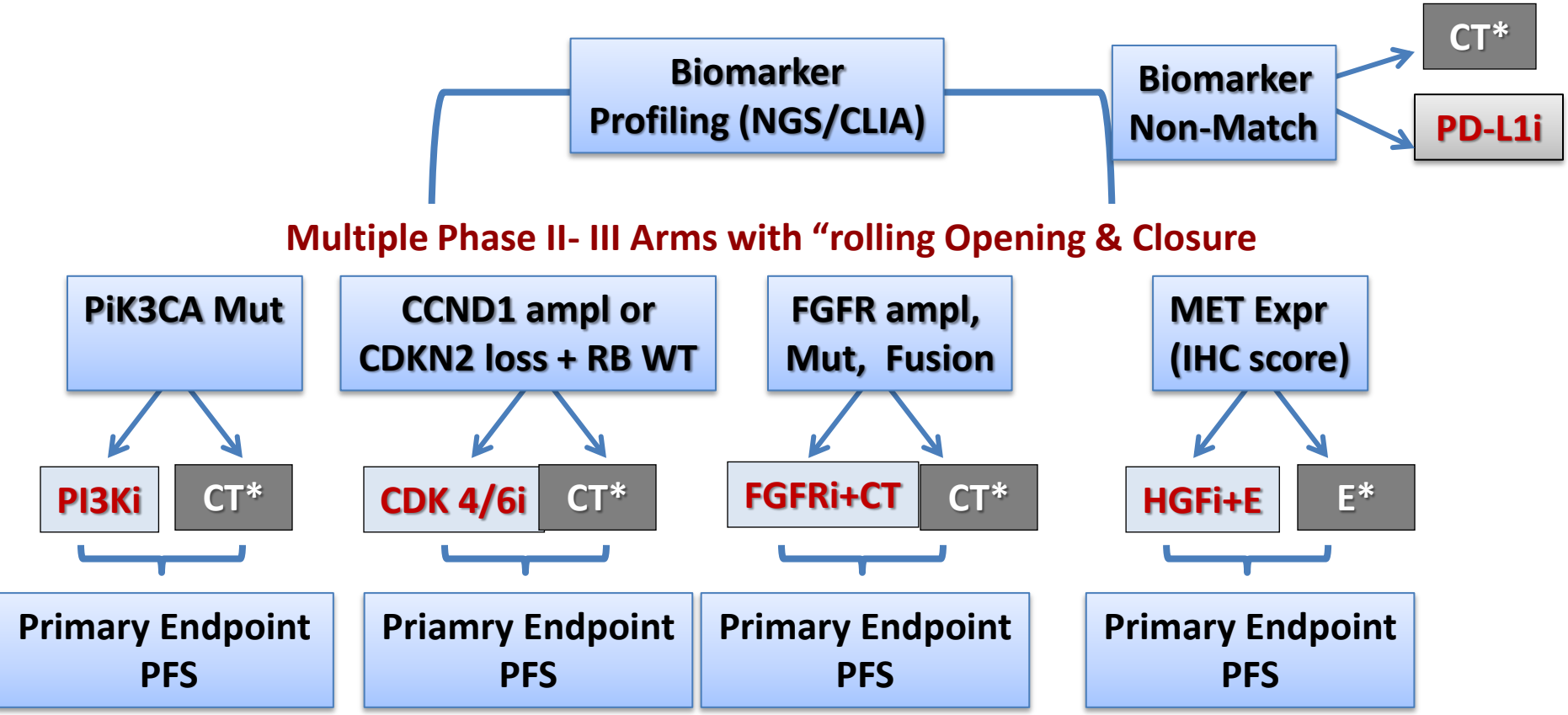

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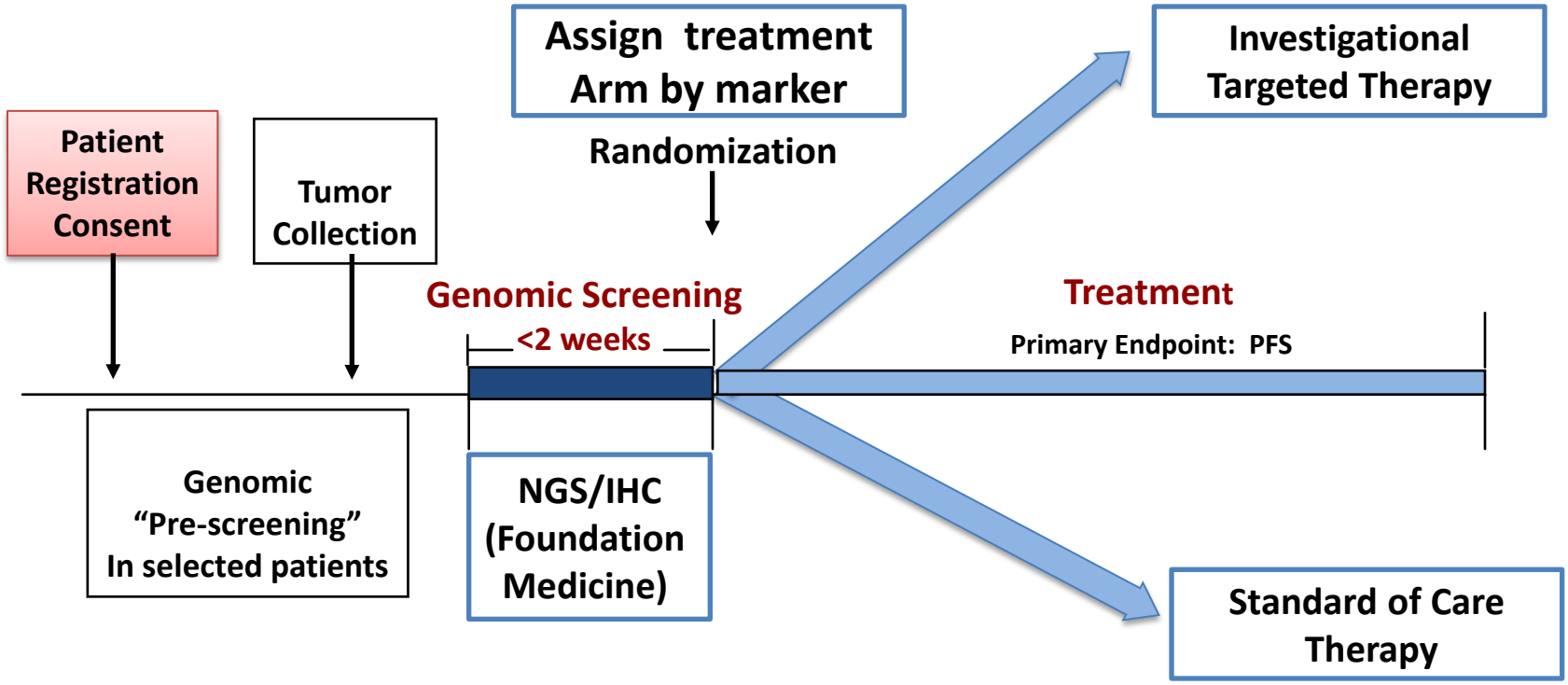
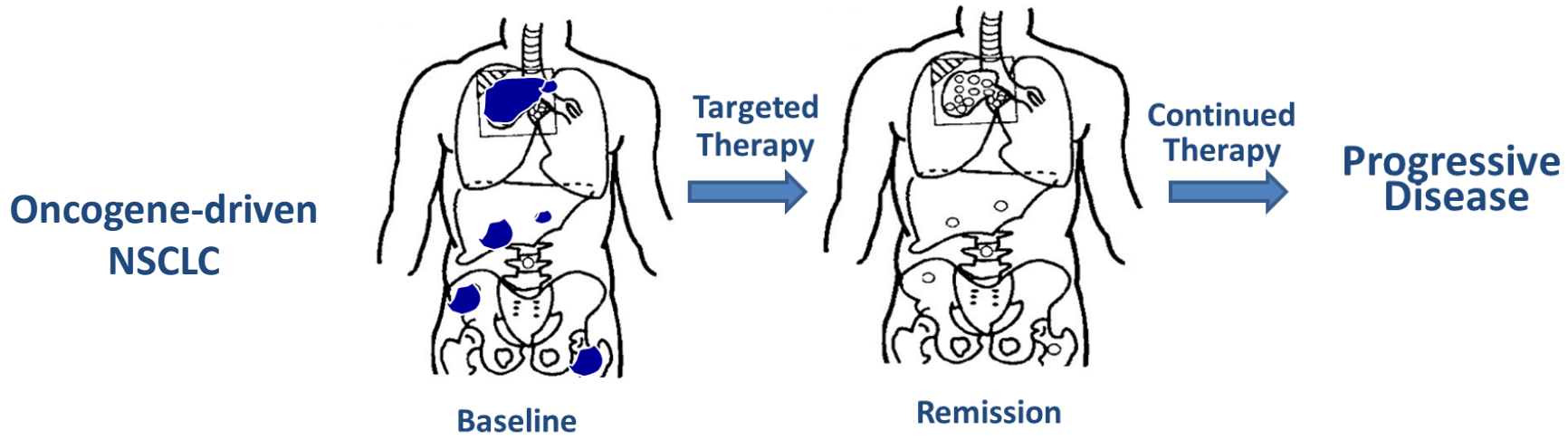
S1400 (MASTER LUNG-1) Squamous Lung Cancer- 2nd Line Therapy



- Organizers: FOCR, NCI-TMSC, FDA, FNIH
- Participants: Entire North American Lung Intergroup (SWOG, Alliance, ECOG-Acrin, NRG, NCI-Canada)
- Screening: ~1,000 patients/year
- With 6 arms open simultaneously, anticipate a "hit rate >60% in matching a patient with a drug/biomarker arm

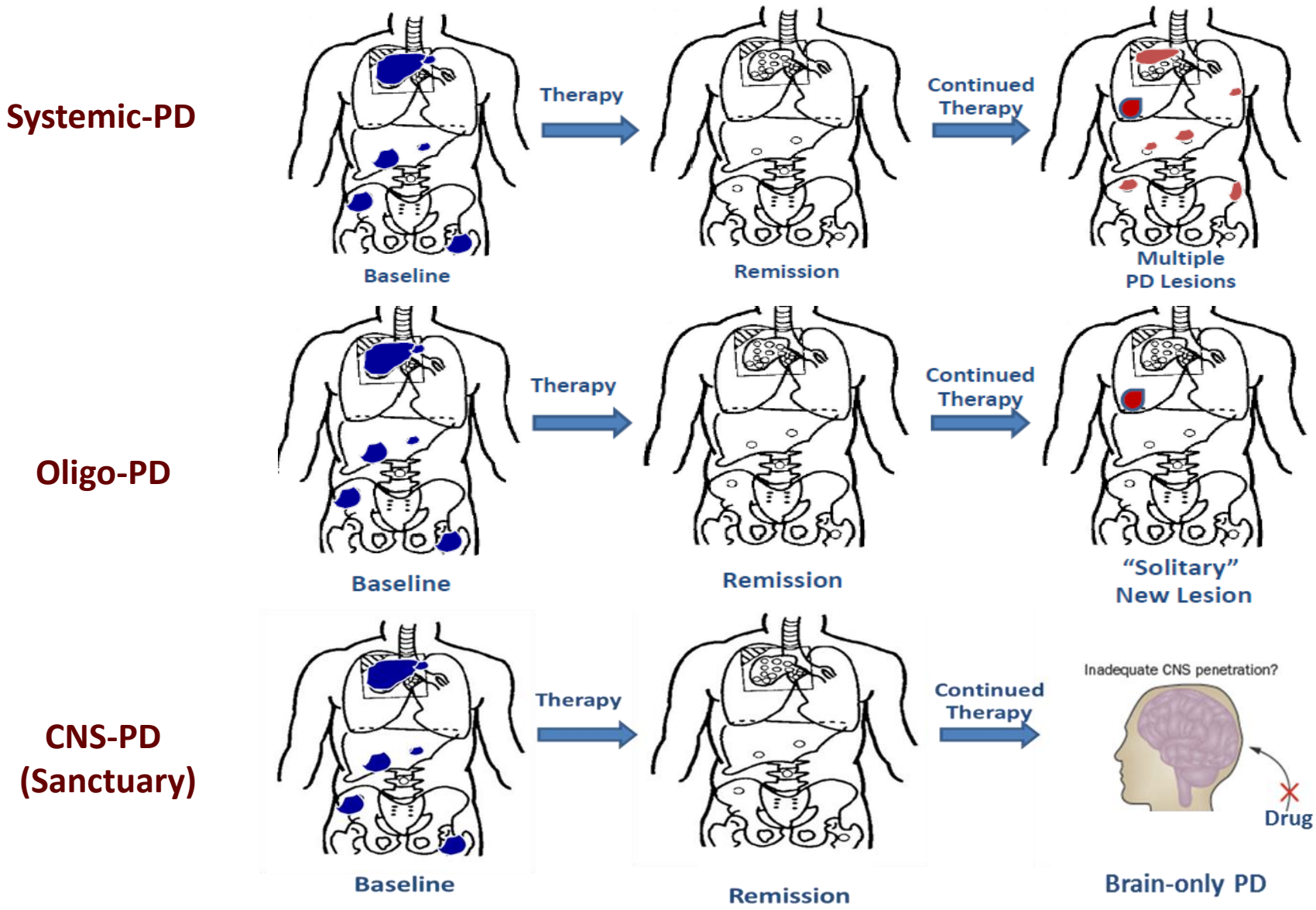
Acquired Resistance to Targeted Therapies in Oncogene-Driven NSCLC: Clinical Practice & Clinical Trials

- Targeted Therapies against Oncogene-Driven Cancers [EGFR mutation+ (Erlotinib) or ALK fusion+ (Crizotinib)] improve response and PFS when compared with chemotherapy
- Even in these most sensitive cancers, acquired resistance is ~universal, with PFS averaging ~10-14 months
- The "subtype" of progressive disease (PD) in individual patients varies greatly (Systemic-PD, Oligo-PD and CNS-PD)
- Hypothesis: "Best" management options at the time of PD varies greatly dependent on the PD subtype (also true for clinical trial designs)



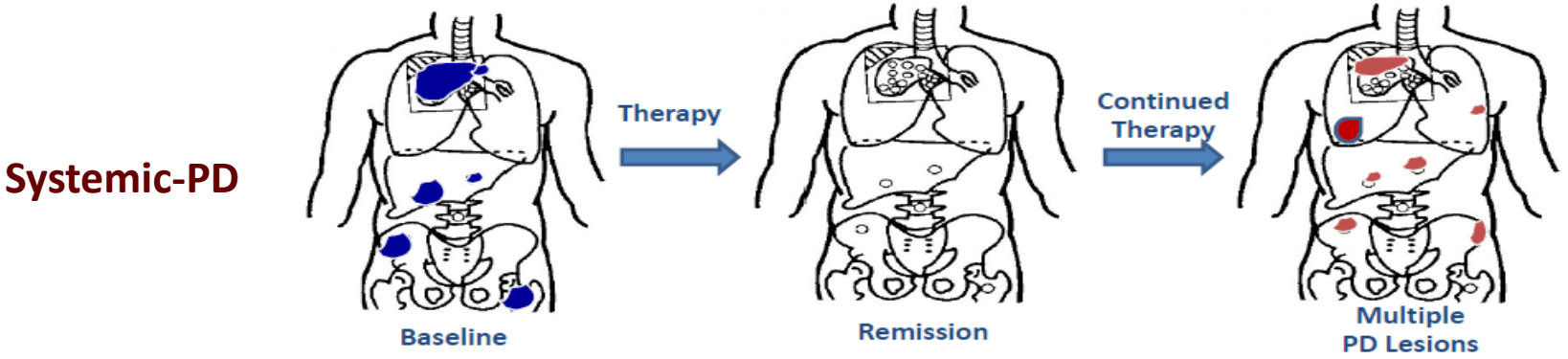
Gandara, Redman et al: Clin Lung Cancer 2014

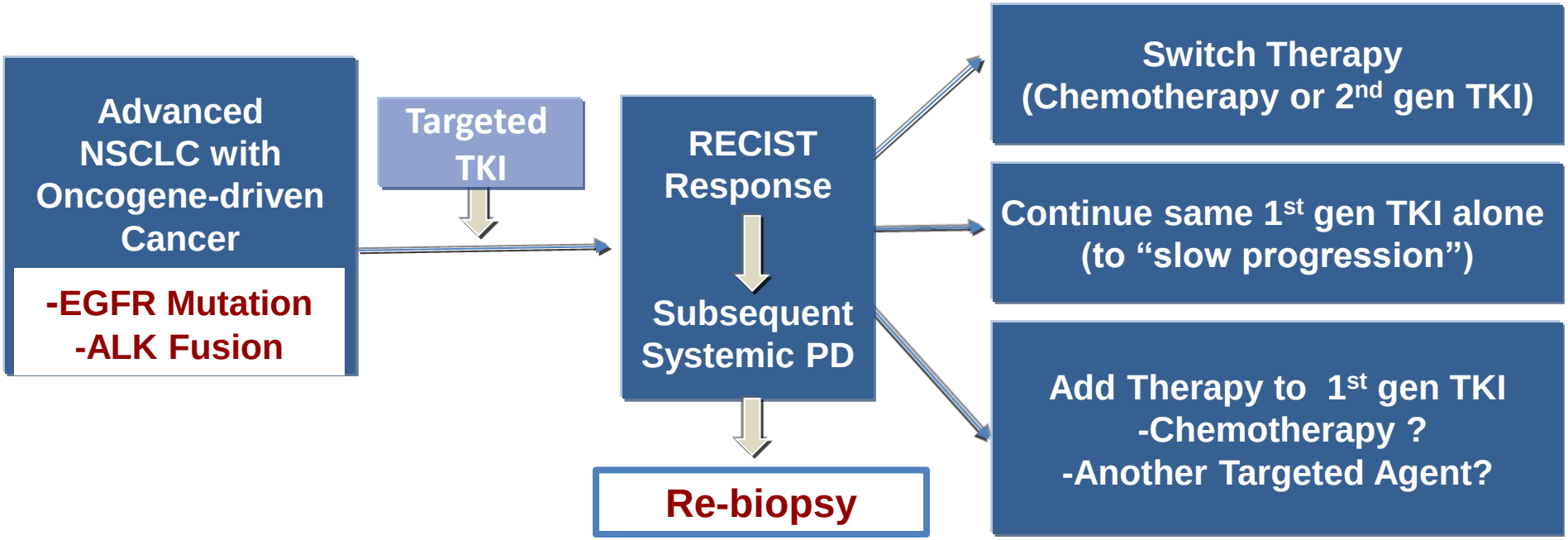
Acquired Resistance to Targeted TKIs: PD Subtype influences Clinical Practice & Clinical Trial Design



Gandara, Redman et al: Clin Lung Cancer 2014

Clinical Trial Designs addressing Acquired Resistance in Oncogene-Driven NSCLC with Systemic PD





Gandara, Redman et al: Clin Lung Cancer 2013

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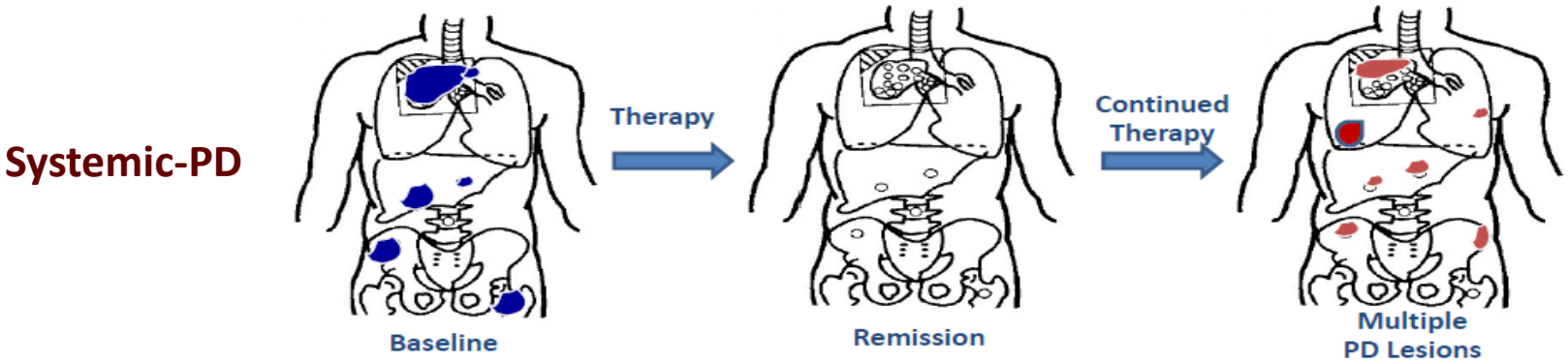
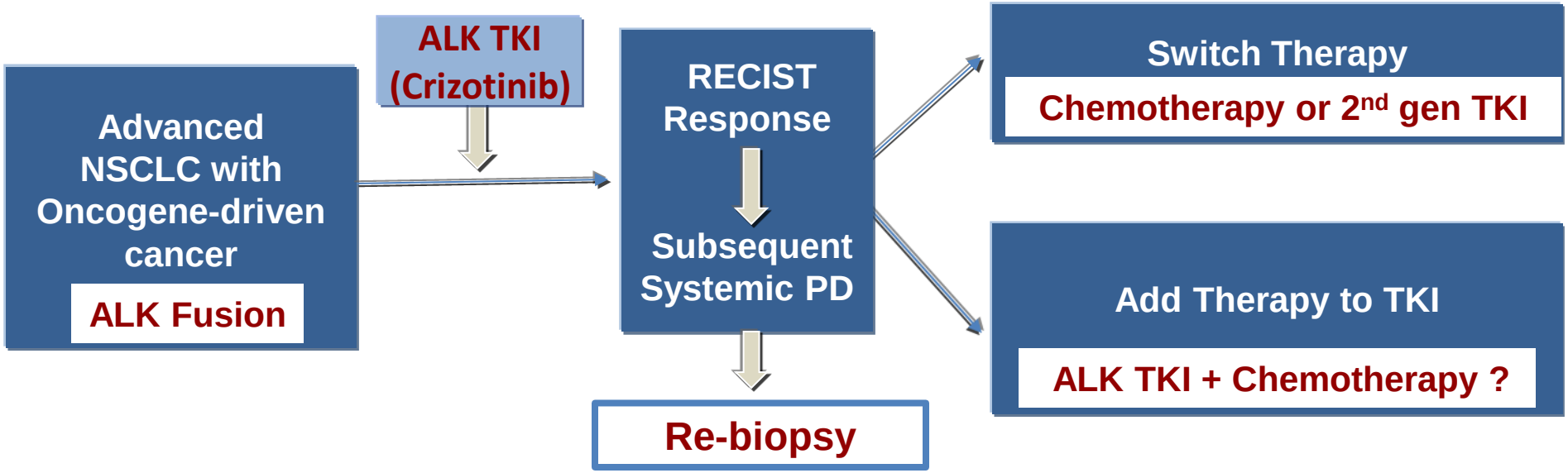




Gandara, Redman et al: Clin Lung Cancer 2014

S1300: SWOG/Intergroup Phase II Trial in ALK-positive NSCLC progressive after Crizotinib

Adv Stage NSCLC

ALK-positive by break-apart FISH

PD on Crizotinib after prior clinical benefit (CR/PR or SD >3 mos)

Pemetrexed-naive

30% Biopsy each arm

Crizotinib + Pemetrexed

Pemetrexed

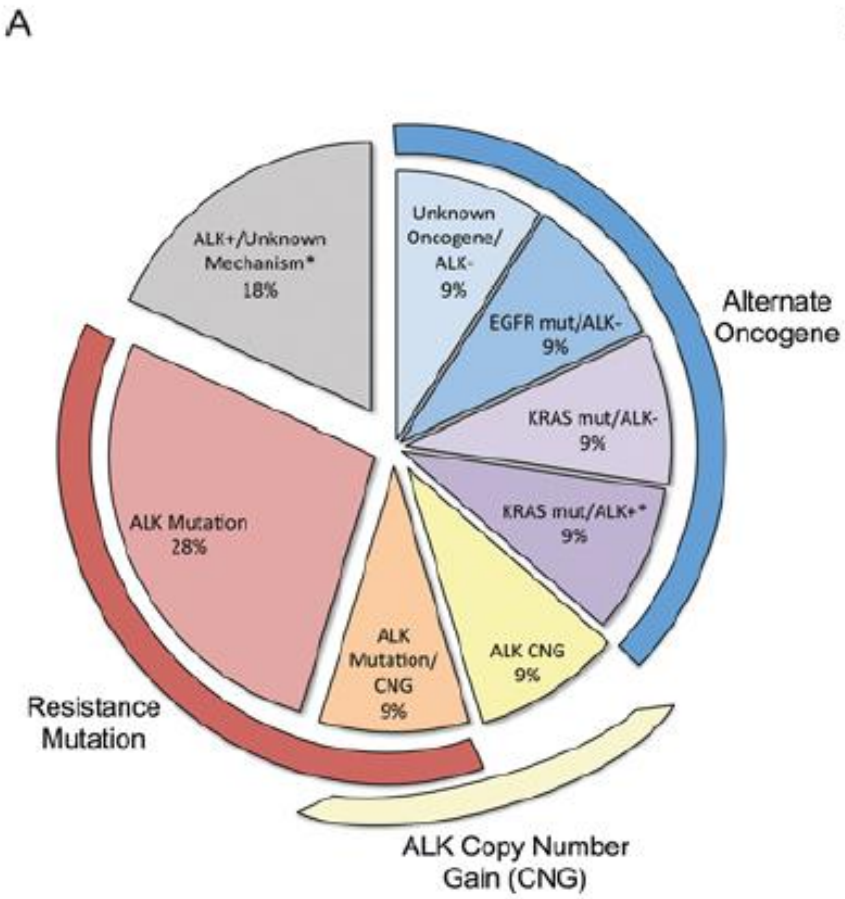
Primary endpoint: PFS

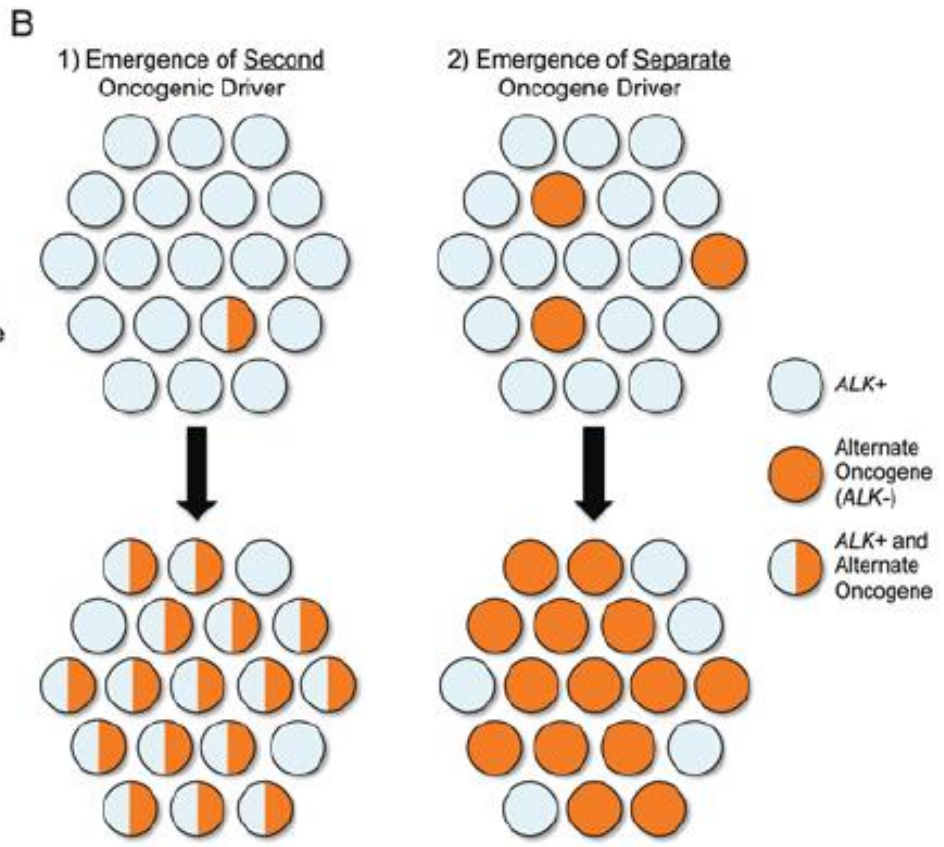
Co-Primary Endpoints:
1) PFS overall + 2) ORR in Pemetrexed arm

Secondary:
ORR, DCR, OS
Patterns of Failure
Toxicity
Translational Studies
(Mechanisms of resistance)

PIs:
R. Camidge, T. Li & R. Doebele

Emergence of ALK Resistance Mechanisms after Crizotinib





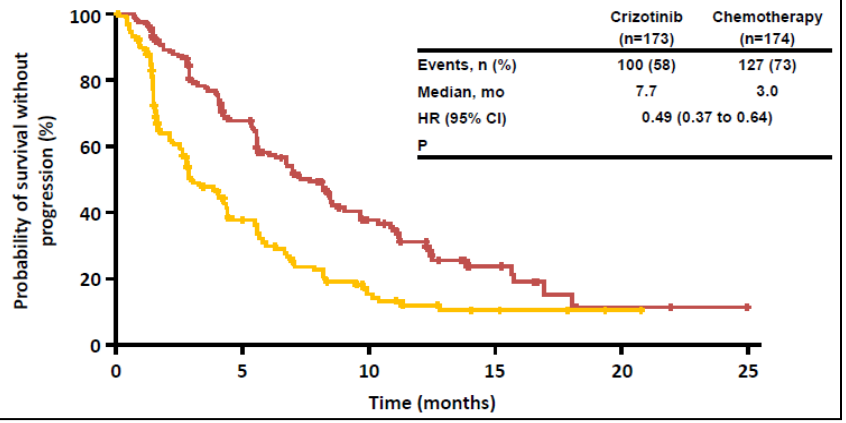
- **Secondary resistance ALK mutations**
- **ALK Gene copy number increase**
- **Transition to EGFR mutation**
- **Transition to KRAS mutation**

Consistent with mathematical models of Evolutionary Biology

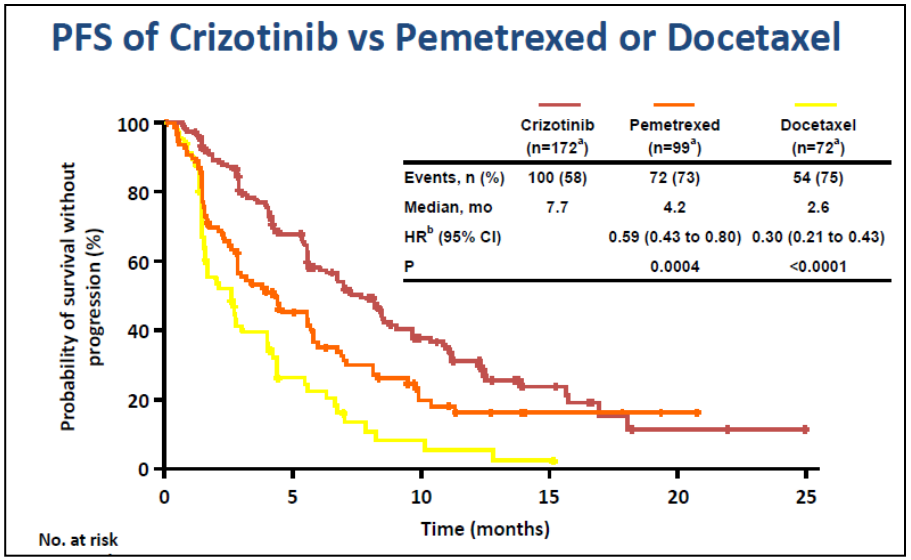
Doeble, Camidge et al: CCR 2012

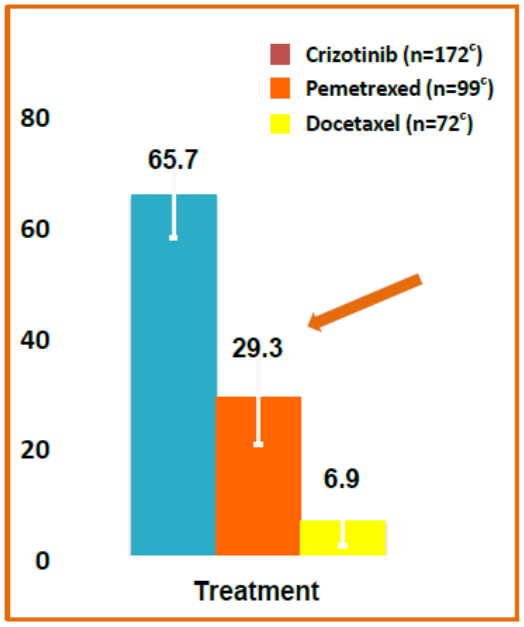
Trial 1OO7: Crizotinib vs Chemotherapy in ALK+ NSCLC

Primary Endpoint: PFS

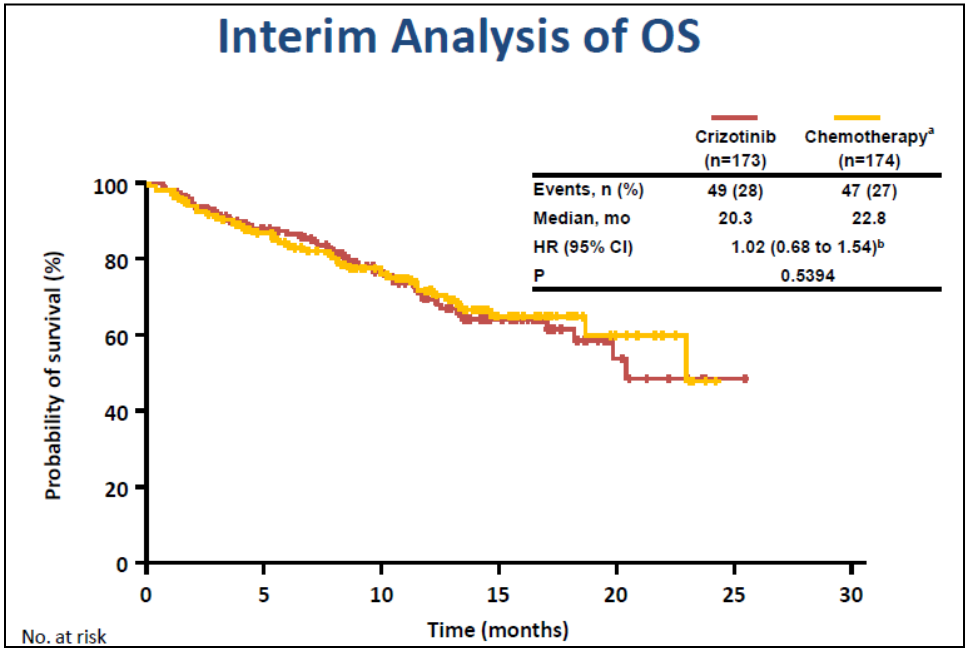


PFS of Crizotinib vs Pemetrexed or Docetaxel



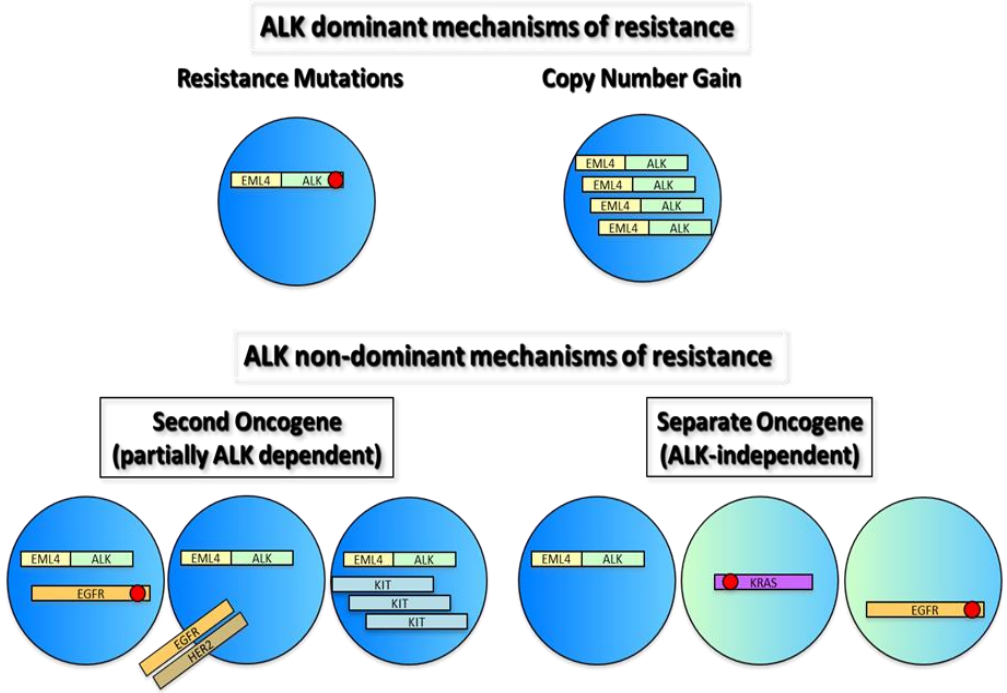


Interim Analysis of OS



Shaw et al: NEJM 2013

S1300: SWOG/Intergroup Phase II Trial in ALK-positive NSCLC progressive after Crizotinib



30% Biopsy each arm

Crizotinib + Pemetrexed

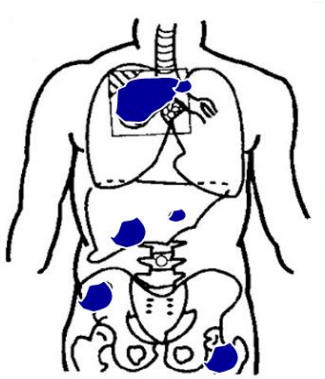
Pemetrexed

Secondary:
ORR, DCR, OS
Patterns of Failure
Toxicity
Translational Studies
(Mechanisms of resistance)

PIs:
R. Camidge, T. Li & R. Doebele

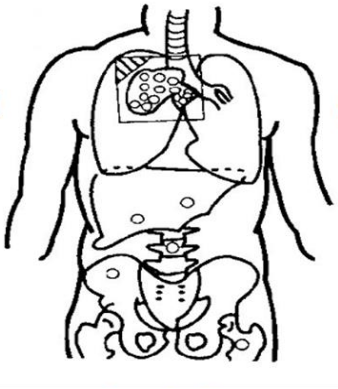
Clinical Trial Designs for Circumvention (Prevention or Delay) of Acquired Resistance in Oncogene-Driven NSCLC

Oncogene-driven NSCLC



Baseline

Targeted Therapy



Remission

Continued Therapy

Prolongation of Remission (delay time to PD)

Advanced Stage NSCLC

Biopsy

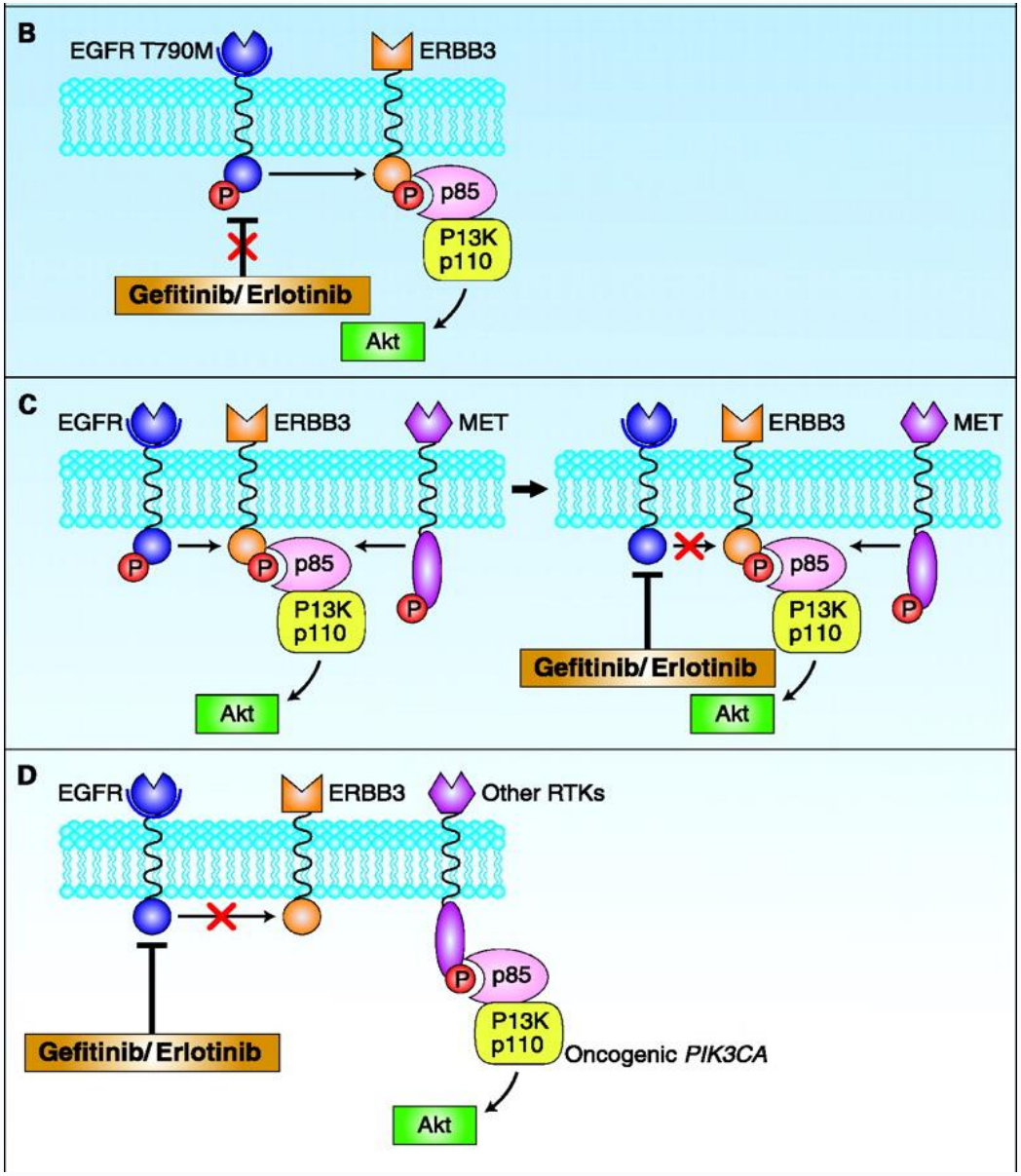
Identification of Driver Oncogene

EGFR Mutation

- Targeted TKI Monotherapy (Standard of Care)
- Targeted TKI Monotherapy (2nd generation agent)
- Sequential TKI Monotherapy (1st gen→2nd generation agent)
- Multi-drug Targeted Therapy

from Gandara, Redman et al: Clin Lung Cancer 2013 (in Press)

Mechanisms of EGFR TKI Resistance (Selected)

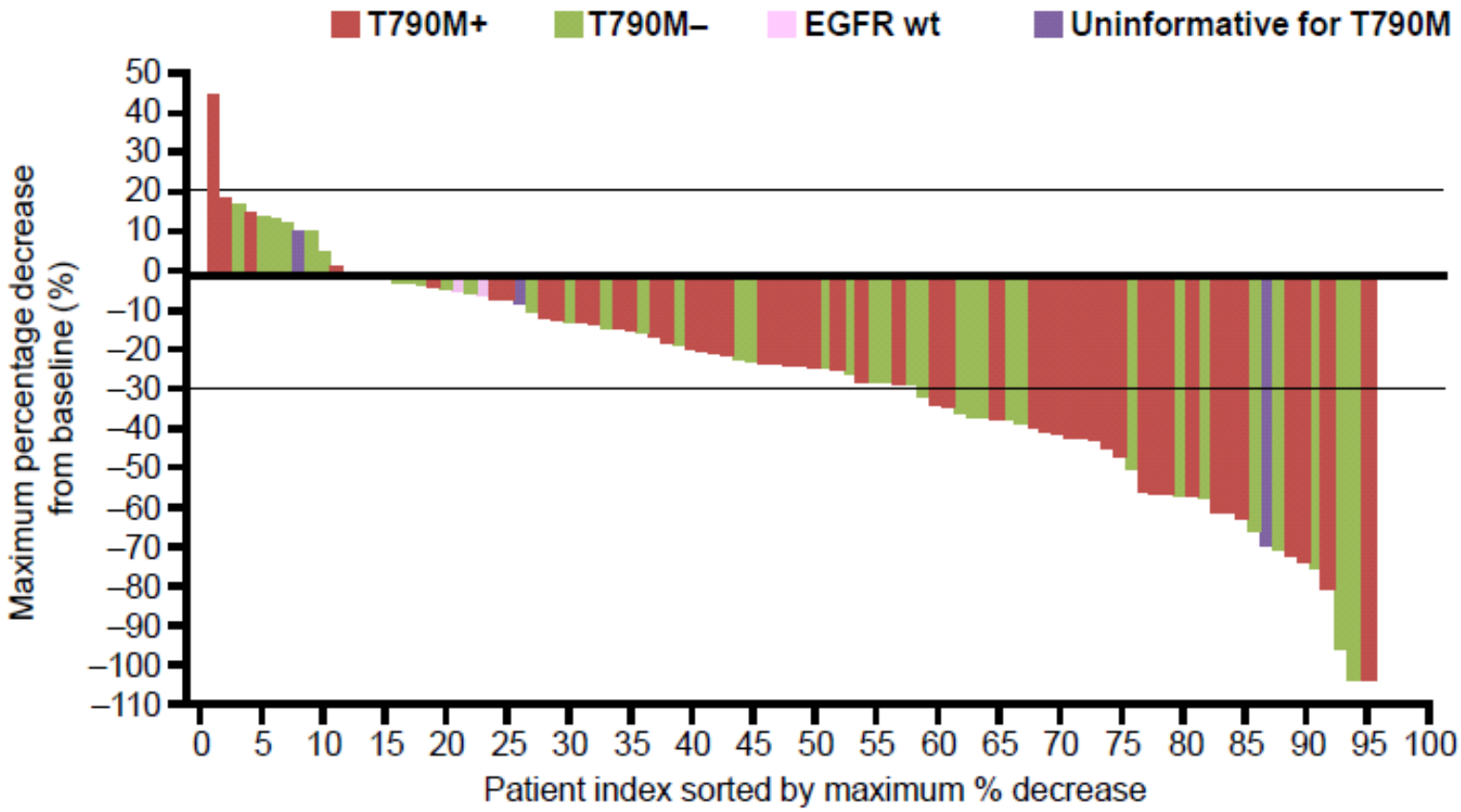


adapted from Engelman et al

- **Secondary EGFR mutation (i.e. T790m)**
  - 2nd Gen EGFR TKIs
    - i.e. Afatinib
  - 3rd Gen- Afatinib/Cetuximab
    - AZ9291, CO1686
- **Bypass signaling via ERBB3**
  - Anti-ERBB3 drugs
    - i.e. MM151 MoAB
- **MET over-expression**
  - MET Inhibitors
    - i.e. MET-Mab (MoAB)
    - ARQ197 (TKI)
- **PIK3CA Mutation/AKT**
  - i.e. BKM120 (PIK3CA)
  - i.e. MK2206 (AKT)

& Others → HSP inhibitors
- i.e. Ganetespib
- AUY922

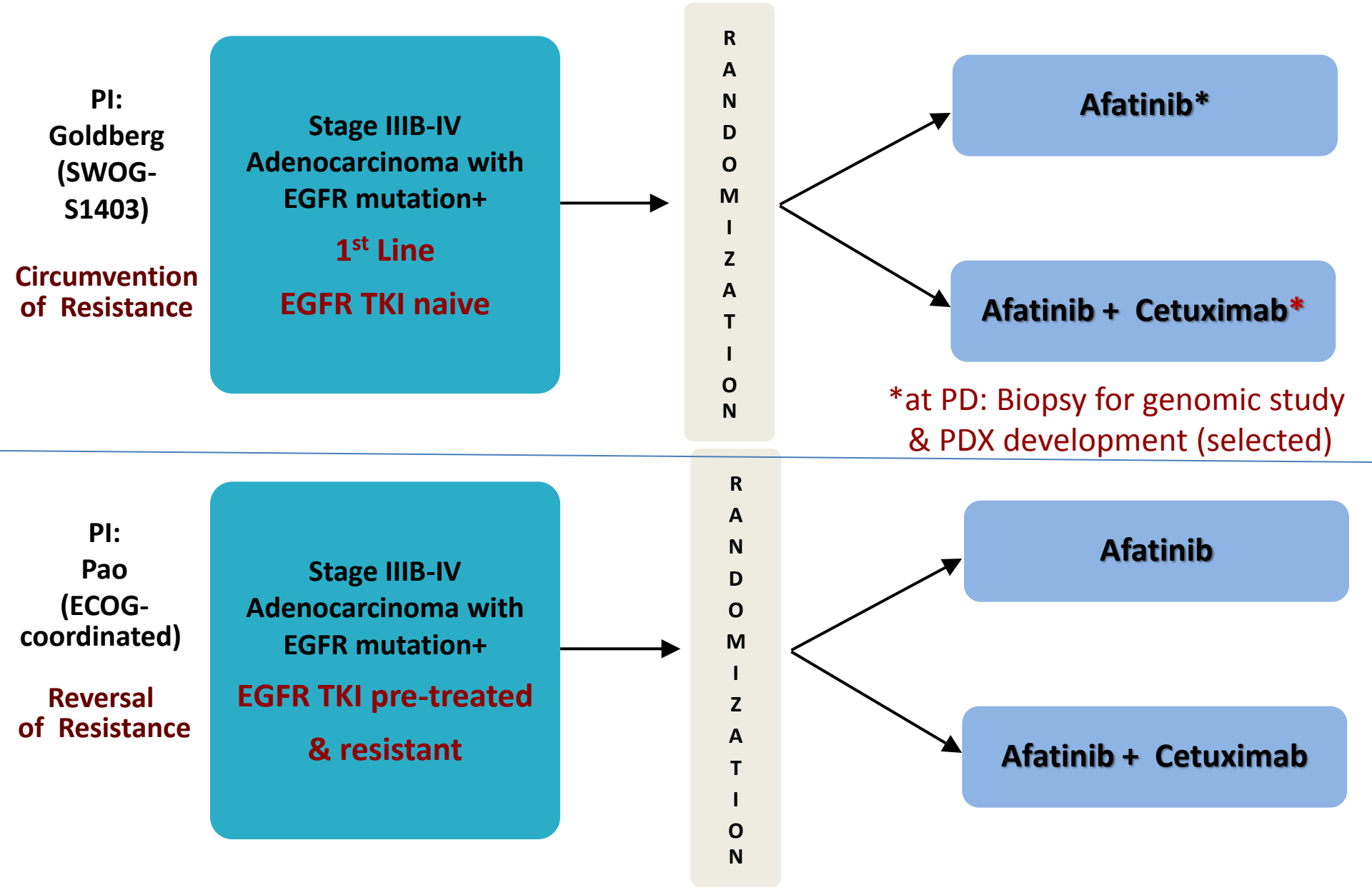
Afatinib + Cetuximab in EGFR-mutated NSCLC refractory to EGFR TKI



Response rate: 30%
Clinical benefit (DCR): 75%

Janjigian, et al. ESMO 2012

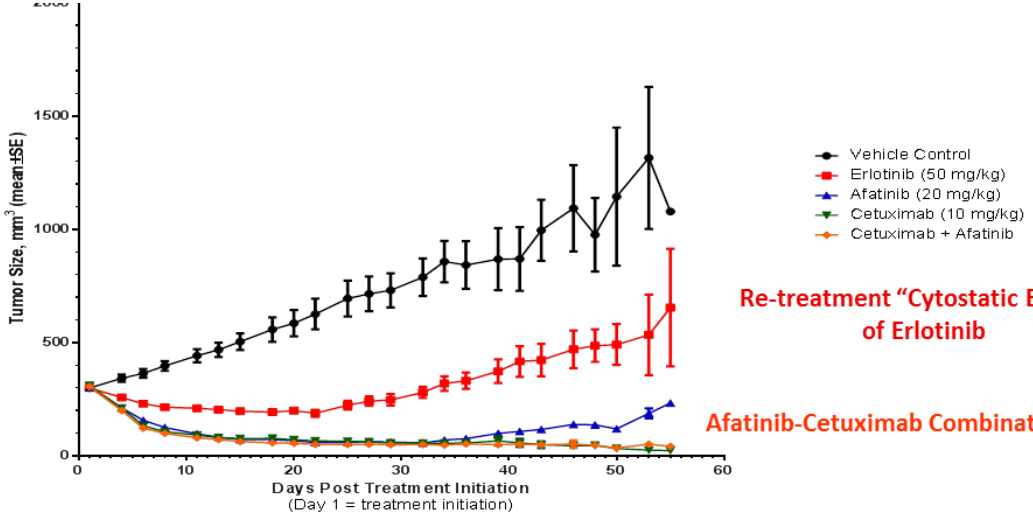
Developing Randomized trials: Afatinib +/- Cetuximab in EGFR mutation+ NSCLC (North American Intergroup)



Afatinib-Cetuximab in EGFR mutant & Erlotinib Acquired Resistance PDX Models:

Results in PDX models mimic the clinical response to Aftatinib-Cetuximab

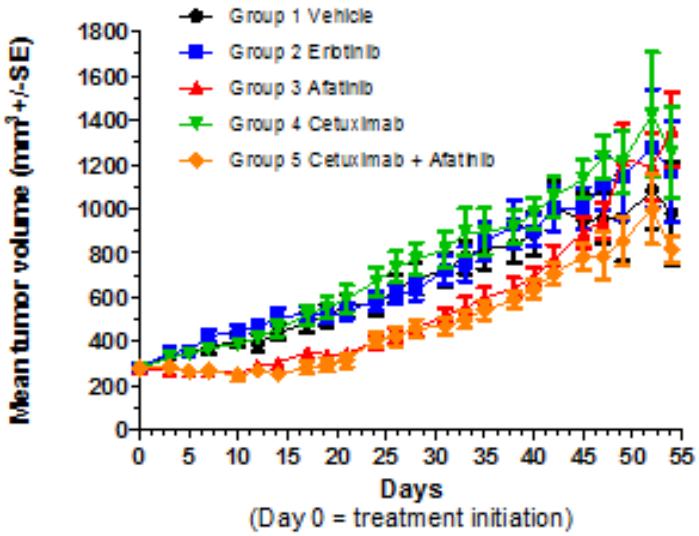
LG0703: EGFR TKI resistant (L858R + High MET. T790M negative)



Re-treatment "Cytostatic Effect" of Erlotinib

Afatinib-Cetuximab Combinations

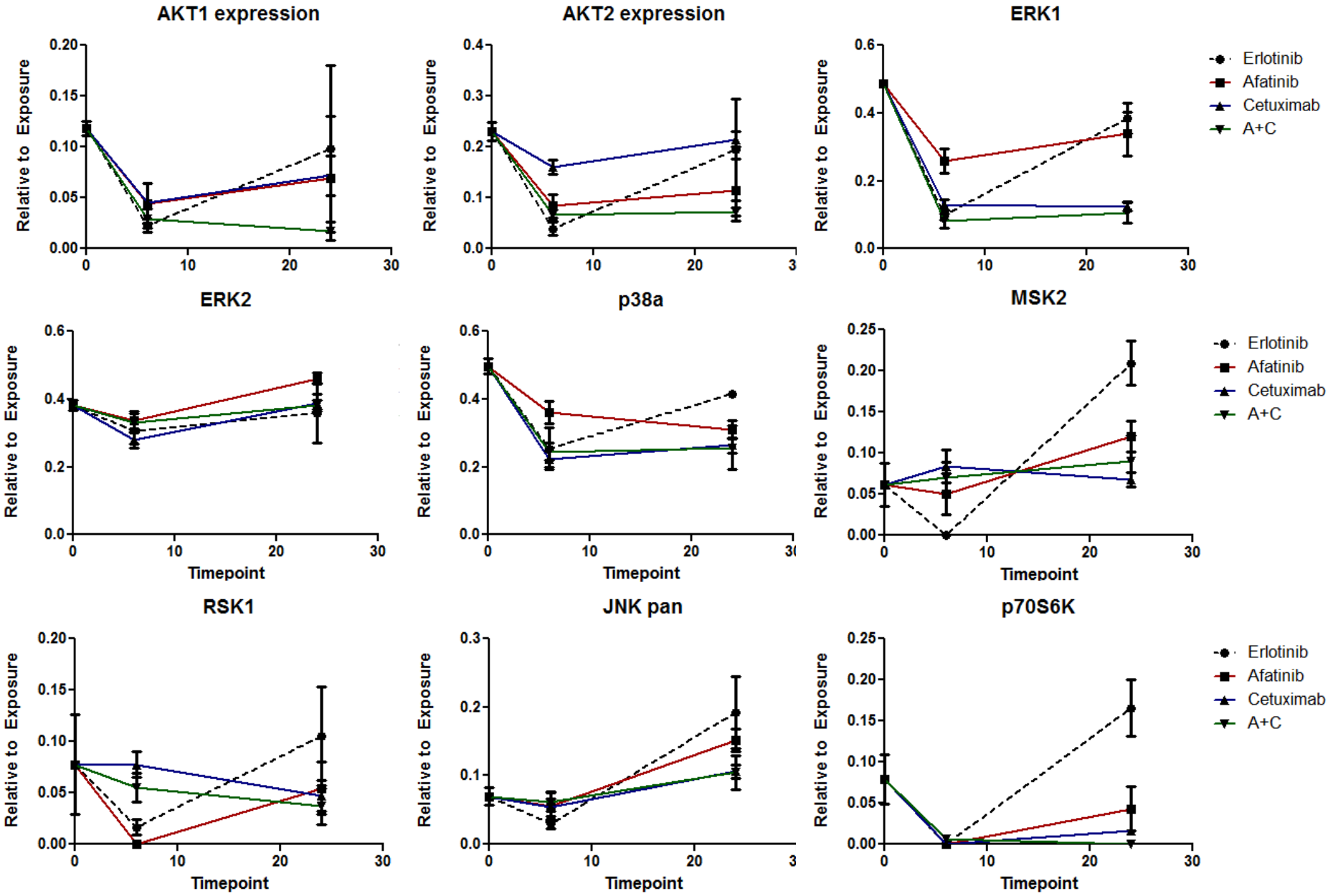
LG1049: EGFR TKI resistant (E19del + T790M positive)



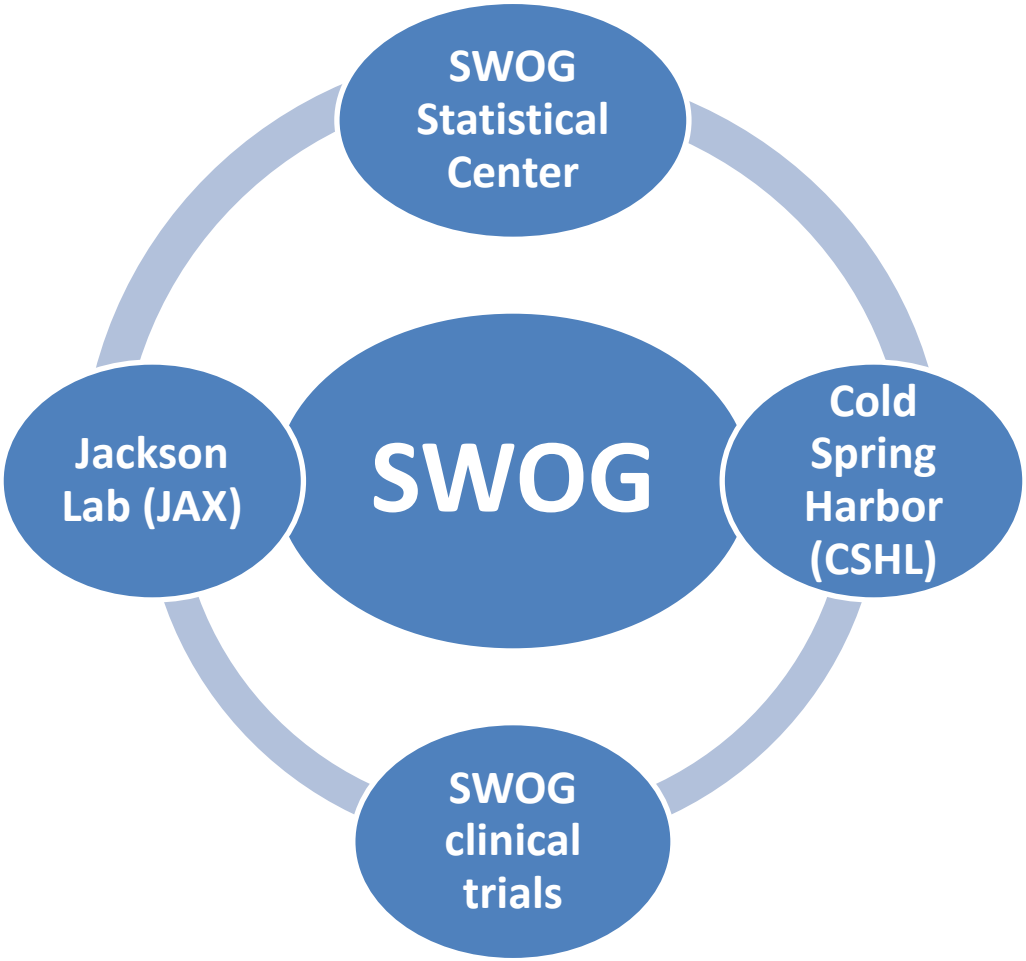
Next Generation Sequencing & Signaling Pharmacodynamics
Pre- & Post-Therapy
to determine & characterize Mechanisms of Sensitivity/Resistance

From Mack, Gandara et al: ASCO 2013

Time-dependent treatment effects on signaling pharmacodynamics (LG703)



SWOG Translational Science Center: Pilot PDX Project in S1403



Summary: Integrating Predictive Biomarkers in Clinical Trial Design

- Master Protocol Designs may provide operational efficiencies to speed up drug-biomarker development & approval, including for drugs directed against uncommon genotypes
- Despite advances with targeted TKIs in Oncogene-driven NSCLC no patients are cured and acquired/adaptive resistance is ~universal
- Subtyping PD into clinically relevant categories should assist in both clinical trial design & day-to-day patient management
- Methods to identify mechanisms of acquired resistance & how to overcome them (or circumvent them) are needed
- Clinical Trial designs will need to account for inter- and intra-patient tumor heterogeneity & the most likely mechanisms of resistance
- Clinically & genomically annotated PDX resources may assist in achieving this latter goal