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

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Disclosures

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• 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

**Predictive Marker**
- Information on disease outcome related to a specific treatment

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

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-

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)

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

T1: Standard Therapy
T2: New (Experimental) Therapy

Hoering, Crowley et al: CCR, 2008
Phase II Trial of Erlotinib +/- MetMab: PFS & OS

Targeted Agents can do harm in the wrong patient population
Evolution of NSCLC Subtyping from Histologic to Molecular-Based

Li, Gandara et al: JCO 2013 (adapted from Pao et al)
Integration of Biomarkers into Clinical Practice: Past, Current & Future

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

2. Molecular Diagnosis:
   - Archival FFPE tumor specimens
   - Archival cancer specimens
   - Macro- or Micro-dissection of Tumors
   - Extract tumor nucleic acids:
     - DNA and RNA
   - 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

   - 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

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

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

*In combination with platinum-based chemotherapy versus chemotherapy

**EGFR IHC positive

Biomarker-driven Clinical Trial Designs (selected)

**Marker Positive (Enrichment) Design**

- **Randomization**: Marker Tested → Marker Positive
- **Assignment**: Standard Therapy → Marker Positive
- **Assignment**: Exp Therapy → (Target Agent or Standard + Target)

**Marker-Based Strategy Design**

- **Randomization**: Marker Tested → Exp Therapy Arm
- **Assignment**: Exp Therapy Arm → Marker + Strategy
- **Assignment**: Standard Therapy Arm → Marker - Strategy
- **Assignment**: Mixture of M+ & M- patients

**Predictive Biomarker Validation (“Treatment by Marker Interaction”)**

- **Stratify**: Marker + → Randomize Standard
- **Stratify**: Marker - → Randomize Exp Therapy

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*
Begin enrollment
Complete accrual (N=648)
Full study unblinded

Primary Endpoint: Improved OS
Overall study α=0.04

Co-Primary Endpoint: Improved OS
Marker+ group α=0.01

Primary Endpoint (No biomarker): Improved OS
Overall study α=0.05

Standard Tx + placebo (N=324)
Standard Tx + New Drug (N=324)

Stage 1: Marker training
-randomly select ½ the pts
-test markers
-define predictive markers

Stage 2: Marker validation
-classify remaining ½ pts by marker
-unblind outcome

Marker identified

Marker not identified

Biomarker analysis dropped

From J Heymach
Integrated New Drug-New Biomarker Development Paradigm:

**Phases of Development of a New Drug**
- Pre-clinical
- Phase I: N=30 (~18 mo.)
- Phase II: N=300 (~18 mo.)
- Phase III: N=1600 (~36 mos)
- Total Time: ~90 mos (7.5 years)

**Phases of Development of New Biomarker linked to New Drug**
- Confirm Target
- Integrate Biomarker
- Biomarker Informative?
- Clinical Validation
- Clinical Application of Biomarker

*from Gandara et al: Clin Lung Cancer, 2012*
Unmet Needs in Future NSCLC Clinical Trials when viewed as a Multitude of Genomic 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** represents 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)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Event Type</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>CDKN2A</td>
<td>Deletion/Mutation/Methylation</td>
<td>72%</td>
</tr>
<tr>
<td>PI3KCA</td>
<td>Mutation</td>
<td>16%</td>
</tr>
<tr>
<td>PTEN</td>
<td>Mutation/Deletion</td>
<td>15%</td>
</tr>
<tr>
<td>FGFR1</td>
<td>Amplification</td>
<td>15%</td>
</tr>
<tr>
<td>EGFR</td>
<td>Amplification</td>
<td>9%</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>Amplification/Mutation</td>
<td>9%</td>
</tr>
<tr>
<td>CCND1</td>
<td>Amplification</td>
<td>8%</td>
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<td>DDR2</td>
<td>Mutation</td>
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<tr>
<td>BRAF</td>
<td>Mutation</td>
<td>4%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Amplification</td>
<td>4%</td>
</tr>
<tr>
<td>FGFR2</td>
<td>Mutation</td>
<td>3%</td>
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</table>
S1400: MASTER LUNG-1: Squamous Lung Cancer- 2nd Line Therapy

Biomarker Profiling (NGS/CLIA)

Multiple Phase II-III Arms with “Rolling Opening & Closure

Biomarker A

Biomarker B

Biomarker C

Biomarker D

Primary Endpoint PFS

Primary Endpoint PFS

Primary Endpoint PFS

Primary Endpoint PFS

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

Project Chair: V. Papadimitrakopoulou
Steering Committee Chair: R. Herbst
SWOG Lung Chair: D. Gandara
S1400: MASTER LUNG-1: Squamous Lung Cancer- 2\textsuperscript{nd} Line Therapy

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

Primary Endpoint
PFS

Primary Endpoint
PFS

Primary Endpoint
PFS

Primary Endpoint
PFS

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

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

Systemic-PD

Oligo-PD

CNS-PD (Sanctuary)

Gandara, Redman et al: Clin Lung Cancer 2014
Clinical Trial Designs addressing **Acquired Resistance in Oncogene-Driven NSCLC with Systemic PD**

- **Advanced NSCLC with Oncogene-driven Cancer**
  - EGFR Mutation
  - ALK Fusion

- **Targeted TKI**

**RECIST Response**

- **Subsequent Systemic PD**
  - **Switch Therapy** (Chemotherapy or 2\(^{nd}\) gen TKI)
  - **Continue same 1\(^{st}\) gen TKI alone** (to “slow progression”)
  - **Add Therapy to 1\(^{st}\) gen TKI**
    - Chemotherapy?
    - Another Targeted Agent?

**Gandara, Redman et al: Clin Lung Cancer 2013**
Clinical Trial Designs addressing Acquired Resistance in Oncogene-Driven NSCLC with Systemic PD

Advanced NSCLC with Oncogene-driven cancer
ALK Fusion

ALK TKI (Crizotinib)

RECIST Response
Subsequent Systemic PD

Switch Therapy
Chemotherapy or 2nd gen TKI

Add Therapy to TKI
ALK TKI + Chemotherapy ?

Re-biopsy

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

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

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

Primary endpoint: PFS

Pls: 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 1007: Crizotinib vs Chemotherapy in ALK+ NSCLC

**Primary Endpoint: PFS**

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (n=173)</th>
<th>Chemotherapy (n=174)</th>
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</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>100 (58)</td>
<td>127 (73)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>7.7</td>
<td>3.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.49 (0.37 to 0.64)</td>
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<tr>
<td><strong>P</strong></td>
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**PFS of Crizotinib vs Pemetrexed or Docetaxel**

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (n=172*)</th>
<th>Pemetrexed (n=95*)</th>
<th>Docetaxel (n=72*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>100 (58)</td>
<td>72 (73)</td>
<td>54 (75)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>7.7</td>
<td>4.2</td>
<td>2.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.59 (0.43 to 0.89)</td>
<td>0.30 (0.21 to 0.43)</td>
<td></td>
</tr>
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</table>
| **P**          | 0.0004               | <0.0001            |}

**Interim Analysis of OS**

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (n=173)</th>
<th>Chemotherapy* (n=174)</th>
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</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>49 (28)</td>
<td>47 (27)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>20.3</td>
<td>22.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.02 (0.88 to 1.54)</td>
<td>1.52 (1.13 to 2.02)</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.5394</td>
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</table>

*Shaw et al: NEJM 2013*
S1300: SWOG/Intergroup Phase II Trial in ALK-positive NSCLC progressive after Crizotinib

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

Oncogene-driven NSCLC

Advanced Stage NSCLC

Biopsy

Identification of Driver Oncogene

Targeted TKI Monotherapy (Standard of Care)

Targeted TKI Monotherapy (2nd generation agent)

Sequential TKI Monotherapy (1st gen→2nd generation agent)

Multi-drug Targeted Therapy

Prolongation of Remission (delay time to PD)

Mechanisms of EGFR TKI Resistance (Selected)

- 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

adapted from Engelman et al
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)

Circumvention of Resistance

PI: Goldberg (SWOG-S1403)

Stage IIIB-IV Adenocarcinoma with EGFR mutation+ 1st Line EGFR TKI naive

Afatinib*

Afatinib + Cetuximab*

*at PD: Biopsy for genomic study & PDX development (selected)

Reversal of Resistance

PI: Pao (ECOG-coordinated)

Stage IIIB-IV Adenocarcinoma with EGFR mutation+ EGFR TKI pre-treated & resistant

Afatinib

Afatinib + Cetuximab
Afatinib-Cetuximab in EGFR mutant & Erlotinib Acquired Resistance PDX Models:
Results in PDX models mimic the clinical response to Afatinib-Cetuximab

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

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

- SWOG Statistical Center
- Cold Spring Harbor (CSHL)
- SWOG clinical trials
- Jackson Lab (JAX)

SWOG
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 approximately 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.