Addressing Tumor Molecular Heterogeneity using
A Novel Clinical Trial Design - PANGEA

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Addressing Molecular Heterogeneity

Gastroesophageal Cancer

“Molecular Drivers”
“Oncogene Addiction”

Inter-patient Heterogeneity

Intra-patient Heterogeneity

‘Classic’ Companion Diagnostics

‘Classic’ Biomarker-Driven Trials

Next-Gen Companion Diagnostics

Next-Gen Clinical Trial Designs

Next-Generation Companion Diagnostics & Next-Generation Trials
Addressing Molecular Heterogeneity

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The Gastroesophageal Nomenclature

Esophageal vs. Gastric Adenocarcinoma
7th edition 2010 AJCC/UICC Staging

Sehdev A, Catenacci D. Discov Med 2013
Gastroesophageal Adenocarcinoma
Epidemiology US 2010

Gastric Cancer
• 26,370 new cases/year
• 10,730 deaths/year

Esophageal Cancer
(70% EGJ Adenocarcinoma)
• 16,940 new cases/year
• EGJ 400% increase in the last decades
• 15,690 deaths/year


• Worldwide Gastroesophageal Cancer 2012:
  – >1,000,000 deaths/year
  – 3rd cancer incidence
  – 2nd cancer death

First Line Management of Advanced Gastroesophageal Cancer


BSC = best supportive care;
MTX = methotrexate; S = S-1; A = doxorubicin
F = 5-FU; C/P = cisplatin; I = irinotecan;
E = epirubicin; O = oxaliplatin; D = docetaxel
Molecular Phenotyping - Solid Tumors

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How Gene Alterations Can Cause Cancer

DNA → Transcription → RNA → Translation → protein

ALtered Genes

Code for

ALTERED PROTEINS

CDKN2a
PTEN
RAS
RAF
mTOR
MAPK
AKT

Resulting in

ALTERED PATHWAYS

RAS
RAF
MAPK

CANCER
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Inter-Patient Tumor Heterogeneity

Catenacci D. Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity. *Molecular Oncology* 2014
Mutation Profile: Targeted Multiplex Inter-patient Heterogeneity

1. TP53 mt, ARID1A mt
2. TP53 mt, APC mt
3. MET amp+, TP53 mt, NOTCH1 mt
4. FGFR2 amp+, TP53 mt, E-cadherin mt
5. KRAS amp+, TP53 mt, CDKN2A/B mt
6. PI3KCA mt, PTCH1 mt, MLH1 mt, MSH1 mt
7. HER2 amp+, SRC amp+, TOP1 amp+
8. HER2 amp+, KRAS amp+, AKT amp+, CCNE1 amp+, CCND1 amp+, MCL1 amp+
9. TP53 mt, PIK3CA mt, CTNNB1 mt, SMAD4 mt
10. IGF1R amp+
11. CEBPA mt
12. MET amp+
13. HER2 amp+, PIK3CA mt, PTEN mt, CDK6 amp, TP53 mt
14. MDM2 amp+
15. CDH1 mt
16. Src amp+, AURKA amp+, CCND1 amp+, CDK4 amp+, RICTOR amp+, CDKN2A/B loss, ATM mt
Mutation Profile: Targeted Multiplex
Inter-patient Heterogeneity

1. TP53 mt, ARID1A mt
2. TP53 mt, APC mt
3. MET amp+, TP53 mt, NOTCH1 mt
4. FGFR2 amp+, TP53 mt, E-cadherin mt
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8. HER2 amp+, KRAS amp+, AKT amp+, CCNE1 amp+, CCND1 amp+, MCL1 amp+
9. TP53 mt, PIK3CA mt, CTNNB1 mt, SMAD4 mt
10. IGF1R amp+
11. EGFR amp+, CEBPA mt
12. MET amp+
13. HER2 amp+, PIK3CA mt, PTEN mt, CDK6 amp, TP53 mt
14. MDM2 amp+
15. CDH1 mt
16. Src amp+, AURKA amp+, CCND1 amp+, CDK4 amp+, RICTOR amp+, CDKN2A/B loss, ATM mt
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Baseline Spatial Heterogeneity Revealed by Multi-site NGS Sequencing

Cohort 1
11 patients

Distant Metastasis
Primary

Whole exome sequencing

Gene Mutations
22% in primary only
58% shared
19% in metastasis only

Gene Amplifications
32% in primary only
37% shared
31% in metastasis only

Pectasides…Catenacci. Genomic Heterogeneity as a Barrier to Precision Medicine in Gastroesophageal Adenocarcinoma. 2017 in review
Temporality Heterogeneity: Tumors Evolve Over Time to Develop Treatment Resistance

Misale et al. Cancer Discovery (2014)
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Tumor Heterogeneity: Inter-patient!! How to characterize economically?
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Classic Biomarker-Driven Clinical Trial Designs

“Retrospective - prospective”

“Biomarker-stratified”

“Biomarker population enriched”

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Biomarker-stratified

Catenacci D. Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity. Molecular Oncology 2014
“Biomarker population enriched”

Catenacci D. Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity. Molecular Oncology 2014
“Biomarker population enriched”

eg. ‘TOGA’ trial HER2 amp+

Screened 4000 patients
To get 584 (~20% positive rate)
(and this had ~130 HER2- pts)
“Biomarker population enriched”
eg. ‘Phase I expansions’ → PIK3CA mt
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How do we molecularly profile? Now...NGS (DNA/RNA), MS

Stricker, Catenacci, Seiwert. Semin Oncol 2011
Next-Generation Diagnostics: NGS for Inter-Patient Tumor Heterogeneity

NGS can also provide:
- MSI status
- Mutations/Mb
  - >19mt/Mb

Implications for immunotherapy

Next-Generation Diagnostics: “Liquid Biopsy”
ctDNA NGS for Intra-Patient Tumor Heterogeneity
Next-Generation Diagnostics: Mass Spec for Inter-Patient Tumor Heterogeneity

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“Exploratory Platform”

“Expansion Platform Type IA – ‘Global’/Compartmentalized”
  • Histology Dependent

“Expansion Platform Type IB – ‘Global’/Compartmentalized”
  • Histology Agnostic

“Expansion Platform Type IIA – ‘Grass-roots’/Holistic”
  • Histology Dependent
    • Without Biologic Beyond Progression
    • With Biologic Beyond Progression

“Expansion Platform Type IIB ‘Grass-roots’”
  • Histology Agnostic

Catenacci D. Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity. Molecular Oncology 2014
“Exploratory Platform”
Eg. ‘I-SPY’, ‘BATTLE’

→ Umbrella: Biomarker Stratified (if control included)
“Expansion Platform Type IA – Global/Compartmentalized”

e.g. ‘FOCUS - Colon’

Expansion Platform Design
Type A - Histology Dependent

Umbrella
Molecular Testing

Drug

Drug "V" Beneficial in "A" biomarker?

YES? Randomized 'A'-enriched Phase III

→ Umbrella: Population Enriched

Drug

V Placebo

W Placebo

X Placebo

Y Placebo

Z Placebo

Biomarker

A

B

C

D

E
“Expansion Platform Type IB – Global/Compartmentalized”

Histology Agnostic eg ('NCI-MATCH', 'Signature')

Expansion Platform Design
Type B - Histology Agnostic

Umbrella
Molecular Testing

Drug "V" Beneficial in "A" biomarker? → YES?

Randomized 'A'-enriched Phase III

How? With different tumor types?

→ Umbrella: Population Enriched

Catenacci D. Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity. Molecular Oncology 2014
“Expansion Platform Type IIA – Grass-Roots/Holistic” eg. ‘PANGEA - GEC’

Expansion Platform Design Type IIA
Histology Dependent & Holistic

Umbrella Molecular Testing

Biomarker

Drug

V Placebo  W Placebo  X Placebo  Y Placebo  Z Placebo

Trial Completion - assess the treatment strategy Holistically

Expansion Platform Type IIA – with biologic beyond progression (BBP) eg. ‘PANGEA - BBP’

Regulatory Challenge - because multiple:
- Biomarkers
- Assays
- Drugs
- Lines
- NEW/Different

Intrapatient - space 1° v Met - over time

Trial Completion - assess the treatment strategy Holistically


Catenacci D. Next Generation Clinical Trials: Strategies to Address Tumor Molecular Heterogeneity. Molecular Oncology 2014
**Expansion Platform Type IIB – Grass-Roots/Holistic**
e.g. ‘SHIVA’

**SHIVA:**
- 10 treatment groups
- No placebo – MD choice

N=741
→ 496 (67%) profiled
→ 195 (26%) fit
→ Randomized
→ 99 vs 96
→ NEGATIVE for PFS!

**Trial Completion - assess the treatment strategy Holistically**

**Personized Treatment Strategy Beneficial?**
→ YES?

**Randomized Phase III Comparing Personalized Strategy to Standard**

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Molecular Profiling and Targeted Therapy for Advanced Thoracic Malignancies: A Biomarker-Derived, Multiarm, Multihistology Phase II Basket Trial

Ariel Lopez-Chavez, Anish Thomas, Arun Rajan, Mark Raffeld, Betsy Morrow, Ronan Kelly

ABSTRACT

Purpose
We conducted a basket clinical trial to assess the feasibility of such a design strategy and to independently evaluate the effects of multiple targeted agents against specific molecular aberrations in multiple histologic subtypes concurrently.

Patients and Methods
We enrolled patients with advanced non–small-cell lung cancer (NSCLC), small-cell lung cancer, and thymic malignancies who underwent genomic characterization of oncogenic drivers. Patients were enrolled onto a not otherwise specified arm and treated with standard-of-care therapies or one of the following five biomarker-matched treatment groups: erlotinib for EGFR mutations; selumetinib for KRAS, NRAS, HRAS, or BRAF mutations; MK2206 for PI3CA, AKT, or PTEN mutations; lapatinib for ERBB2 mutations or amplifications; and sunitinib for KIT or PDGFRA mutations or amplification.

Results
Six hundred forty-seven patients were enrolled, and 88% had their tumors tested for at least one gene. EGFR mutation frequency was 22.1% in NSCLC, and erlotinib achieved a response rate of 60% (95% CI, 32.3% to 83.7%). KRAS mutation frequency was 24.9% in NSCLC, and selumetinib failed to achieve its primary end point, with a response rate of 11% (95% CI, 0% to 48%). Completion of accrual to all other arms was not feasible. In NSCLC, patients with EGFR mutations had the longest median survival (3.61 years, 95% CI, 2.89 to 5.5 years), followed by those with ALK rearrangements (2.94 years; 95% CI, 1.66 to 4.61 years), those with KRAS mutations (2.3 years; 95% CI, 2.3 to 2.17 years), those with other genetic abnormalities (2.17 years; 95% CI, 1.3 to 2.74 years), and those without an actionable mutation (1.85 years; 95% CI, 1.61 to 2.13 years).

Conclusion
This basket trial design was not feasible for many of the arms with rare mutations, but it allowed the study of the genetics of less common malignancies.

J Clin Oncol 33. © 2015 by American Society of Clinical Oncology
Inter-patient Heterogeneity
- prioritized algorithm

Intra-patient Heterogeneity
- through space $1^0$ vs Metastases
- over time (resistance)

Planned treatment arms; MET and FGFR2+ patients receiving FOLFOX alone to date.
Expansion Platform Type II

Subgroup

All Patients (ITT)

A
B
C
D
E
F
G
H

Biomarker groups

Treatment

Personalized Tx

Z

Z

Z

Z

Z

Z

Z

Z

Z

S

Z

U

Z

V

Z

W

Z

X

Z

Y

Z

Personalized Tx Better

Standard Tx Better
The PANGEA - IMBBP Trial

Personalized ANtibodies for Gastro-Esophageal Adenocarcinoma: A Pilot 1st Metastatic Trial of Biologics Beyond Progression

Diagnosis: metastatic cancer

Biomarker Evaluation in all samples to allow for treatment assignment

ARM B: Therapy based on molecular profile

Anticipated Incidence

20%
HER2 amplified

7%
MET amplified/Hi

8%
FGFR2 amplified

5/20%
EGFR amplified/Hi
KRAS wild type
NI HER2, FGFR2, RON, MET

KRAS/BRAF/PIK3CA/AKT/PTEN delt/amplified
NI HER2, FGFR2, RON, MET

15/10%

15%
MSI-H, High TMB, EBV+

Historical Control (Arm A) → FOLFOX

FOLFOX

PFS₁
6m

PD1

FOLFIRI

PFS₂
4m

PD1

PFS₃
2m

FOLTAX

PD2

Arm B1
FOLFOX - Trastuzumab

Arm B2
FOLFOX - METab

Arm B3
FOLFOX - FGFR2ab

Arm B4
FOLFOX - EGFRab

Arm B5
FOLFOX - VEGFR2ab

Arm B6
FOLFOX - PD1ab

Arm B7

FOLFIRI

PD1

FOLFIRI + T

PD2

FOLFIRI + M

PD2

FOLFIRI + F

PD2

FOLFIRI + EGFRab

PD2

FOLFIRI + V

PD2

FOLFIRI + PD1

PD2

FOLTAX

PD1

FOLTAX + T

PD2

FOLTAX + M

PD2

FOLTAX + F

PD2

FOLTAX + EGFRab

PD2

FOLTAX + V

PD2

FOLTAX + PD1

PD2

Primary mOS Endpoint (N=68)
Inter-patient Heterogeneity
- prioritized algorithm

Baseline Intra-patient Heterogeneity
$$\frac{9}{28} = 32\%$$

Planned treatment arms; MET and FGFR2+ patients receiving FOLFOX alone to date.
ORR – ITT (excluding MET++/FGFR2++)

<table>
<thead>
<tr>
<th>Biomarker group</th>
<th>N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2++</td>
<td>8</td>
</tr>
<tr>
<td>EGFR++</td>
<td>2</td>
</tr>
<tr>
<td>MSI-H</td>
<td>1</td>
</tr>
<tr>
<td>VEGFR2++</td>
<td>3</td>
</tr>
<tr>
<td>EGFR+</td>
<td>1</td>
</tr>
<tr>
<td>VEGFR2+</td>
<td>1 (not eval--&gt;peritoneal dz not measurable)</td>
</tr>
</tbody>
</table>

13/15 87% ORR

16/16 100% DCR
### ORR₁ and DCR₁

**ITT plan 68 patients (all treated with biologic therapy)**

<table>
<thead>
<tr>
<th>ORR</th>
<th>All pts evaluable for ORR</th>
<th>ORR = 16/20</th>
<th>80%</th>
<th>Historic ORR = 30-45%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Of those treated with biologic therapy:</td>
<td>ORR = 13/15</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Of those NOT treated with biologic therapy (ie MET/FGFR2+):</td>
<td>ORR = 3/5</td>
<td>60%</td>
<td></td>
</tr>
</tbody>
</table>

**DCR**

<table>
<thead>
<tr>
<th>DCR</th>
<th>DCR 16/16</th>
<th>DCR = 100%</th>
<th>Historic DCR = 60-70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Of those treated with biologic therapy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Of those NOT treated with biologic therapy (ie MET/FGFR2+):</td>
<td>DCR 5/5</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

**Interim analysis at 30% of enrolled patients**

**Historic ORR by HER2 + vs -**

| HER2+ pts per PANGEA | ORR HER2+ 8/8 | 100% | HER2+ = 47% (TOGA), vs 35% chemo alone |
| HER2- pts per PANGEA | ORR HER2- 8/12 | 66.70% | HER2- = 30-40% (METGASTRIC, FOLFOX-placebo 40% in Her2- pts) |
| Of those treated with biologic therapy: | ORR HER2- 5/7 | 71% | |
| Of those NOT treated with biologic therapy: | ORR HER2- 3/5 | 60% | |
Primary Endpoint OS

• In a phase IIa pilot study
  – 80% power, one-sided alpha 0.1, HR 0.67 (mOS 18 months)
  • Assuming historical mOS is 12 months (it isn’t)
    – $H_0$: 50% of patients alive at 12 months
    – $H_1$: 63% of patients alive at 12 months
    – Sample size needed: 68 patients (43 alive at 12 months)

• 10/13 (77%) alive 12 months.
The PANGEA -2MBBP Trial

Personalized ANtibodies for Gastro-Esophageal Adenocarcinoma: Phase II Metastatic Biologic Beyond Progression Trial (R 2:1)

**Diagnosis:** metastatic cancer

**Arm A:** Standard Chemotherapy + Placebo

**Biomarker Evaluation in all samples prior to randomization**

**Arm B:** Therapy based on molecular profile

**Stratify:**
- i) Stage
- ii) PS
- iii) Biomarker
- iv) GEJ v distal stomach
- v) Site of metastases

**Primary Endpoint: OS (HR 0.67)**
- i) Arm A v B (N=192, 128-B:64-A )
- ii) Arm A, v B

**Secondary Endpoints:**
- PFS1,2,3, PFS1+2+3, 2nd/3rd line rates
- RR, toxicity,
- Arm A1 v A2, B1 v B2 etc

**Tissue correlates**

**Standard care: Control Arm**

**Arm A1:** HER2 amplified

**Arm A2:** MET amplified/Hi

**Arm A3:** FGFR2 amplified

**Arm A4:** KRAS/PI3K wild type

**Arm A5:** KRAS/BRAF/PIK3CA mt/amp

**Arm A6:** MSI-H, High TMB, EBV+

**Arm B1:** HER2 amplified

**Arm B2:** MET amplified/Hi

**Arm B3:** FGFR2 amplified

**Arm B4:** EGFR/HER3 amplified/Hi

**Arm B5:** KRAS wild type

**Arm B6:** MSI-H, High TMB, EBV+

**FOLFOX + placebo**

**FOLFIRI + placebo**

**FOLFOX-Trastuzumab**

**Arm B1:** HER2 amplified

**Arm B2:** MET amplified/Hi

**Arm B3:** FGFR2 amplified

**Arm B4:** EGFR/HER3 amplified/Hi

**Arm B5:** KRAS wild type

**Arm B6:** MSI-H, High TMB, EBV+

**FOLFOX-METab**

**Arm B1:** HER2 amplified

**Arm B2:** MET amplified/Hi

**Arm B3:** FGFR2 amplified

**Arm B4:** EGFR/HER3 amplified/Hi

**Arm B5:** KRAS wild type

**Arm B6:** MSI-H, High TMB, EBV+

**FOLFOX-FGFR2ab**

**Arm B1:** HER2 amplified

**Arm B2:** MET amplified/Hi

**Arm B3:** FGFR2 amplified

**Arm B4:** EGFR/HER3 amplified/Hi

**Arm B5:** KRAS wild type

**Arm B6:** MSI-H, High TMB, EBV+

**FOLFOX-EGFRab**

**Arm B1:** HER2 amplified

**Arm B2:** MET amplified/Hi

**Arm B3:** FGFR2 amplified

**Arm B4:** EGFR/HER3 amplified/Hi

**Arm B5:** KRAS wild type

**Arm B6:** MSI-H, High TMB, EBV+

**FOLFOX-VEGFR2ab**

**Arm B1:** HER2 amplified

**Arm B2:** MET amplified/Hi

**Arm B3:** FGFR2 amplified

**Arm B4:** EGFR/HER3 amplified/Hi

**Arm B5:** KRAS wild type

**Arm B6:** MSI-H, High TMB, EBV+

**FOLFOX-PD-1ab**

**Arm B1:** HER2 amplified

**Arm B2:** MET amplified/Hi

**Arm B3:** FGFR2 amplified

**Arm B4:** EGFR/HER3 amplified/Hi

**Arm B5:** KRAS wild type

**Arm B6:** MSI-H, High TMB, EBV+

**PFS1**

**PFS2**

**PFS3**

**Primary mOS Endpoint (N>192)**
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Thank you!

Einstein discovers that time is actually money.