Towards personalized treatment for gastroesophageal adenocarcinoma: Strategies to address inter- and intra- patient tumor heterogeneity: PANGEA

D.V.T. Catenacci[1], B. Polite[1], L. Henderson[1], P. Xu[1], G.B. Carey[1], W.L. Liao[1,2], T. Hembrough[2], J. Burrows[2], T. Karrison[3], J. Hart[4], S.Y. Xiao[4], C. Fitzpatrick[4], R. Marsh[1], E.Vokes[1], O.Olopade[1], V. Villaflor[1], R. Salgia[1], H.L. Kindler[1], R.L.Schilsky[1]

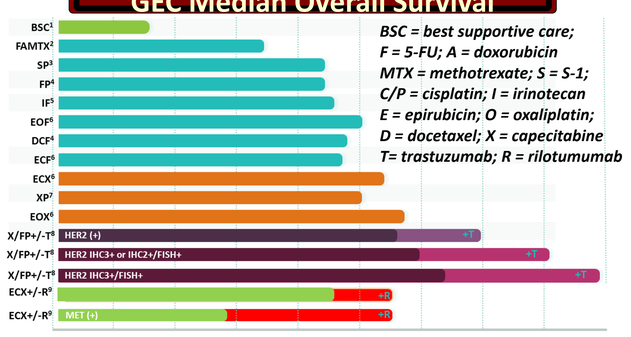
[1]The University of Chicago Medical Center, Section of Hematology/OncologyChicago, IL; [2]Oncoplex Dx Inc. Rockville, MD;
[3]The University of Chicago, Department of Health Studies, Chicago, IL; [4]The University of Chicago, Department of Pathology, Chicago, IL;

Abstract No. 38, Poster Code P4.08 WIN 5th Annual Symposium. Paris, France July 10-12, 2013. Best-Abstract Award and Oral Presentation

Abstract

Gastroesophageal adenocarcinoma (GEC) is the third most common malignancy and second highest cause of cancer mortality worldwide. The promise of 'personalized' cancer care with therapies targeted toward specific molecular aberrations has great potential to improve clinical outcomes. However, there is emerging understanding of profound molecular heterogeneity within GEC (inter-patient heterogeneity), and within an individual (intra-patient heterogeneity) through space (primary tumor to metastatsis) and time (resistance to treatment). This heterogeneity is a hurdle to advancing GEC treatment. Current clinical trial design paradigms are challenged by heterogeneity, as they are unable to test targeted therapeutics against low frequency genomic aberrations with adequate power. Accrual difficulties to GEC trials are exacerbated by low frequencies of molecular 'oncogenic drivers'. Oncogenic drivers of GEC including MET, FGFR2, and others, have even less frequent genomic activation than HER2 (10-20%). To address this recognized challenge, there is need for novel clinical trial designs/strategies implementing medium throughput technologies in order to account for inter-patient molecular diversity. Importantly, there is also need for predefined treatment algorithms given multiple aberrations observed within any one individual. Finally, access to multiple therapeutic agents is required to be available for treatment. Intra-patient heterogeneity may be addressed by post-treatment biopsy and repeating the 'biomarker and treatment assignment algorithm'. We present an innovative clinic trial design, PANGEA (Personalized Anti-Neoplastics for Gastro-Esophageal Adenocarcinoma), that integrates novel medium throughput proteomic and genomic technologies with a practical 'biomarker assay and treatment algorithm', randomizing patients to 'personalized treatment' versus standard of care for metastatic GEC. Data from GEC patients having undergone biomarker assessment and mock treatment assignment on a pilot feasibility phase of the trial will also be presented.

GEC Median Overall Survival



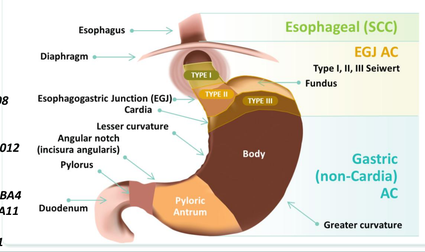
BSC = best supportive care;
F = 5-FU; A = doxorubicin
MTX = methotrexate; S = S-1;
C/P = cisplatin; I = irinotecan
E = epirubicin; O = oxaliplatin;
D = docetaxel; X = capecitabine
T= trastuzumab; R = rilotumumab

First Line Therapy

1. Murad, et al. Cancer 1993
2. Vanhoefer, et al. JCO 2000
3. Ajani, et al. ASCO 2009
4. Van Cutsem, et al. JCO 2006
5. Dank, et al. Ann Oncol 2008
6. Cunningham, et al. NEJM 2008
7. Kang, et al. Ann Oncol 2009
8. Bang, et al. Lancet 2010
9. Oliner et al. J Clin Oncol 30, 2012 (suppl; abstr 4005)

Second/Third Line Therapy

1. Ford et al. J Clin Oncol 2012 LBA4
2. Bang et al. J Clin Oncol 2012 A11
3. Kang et al. JCO 2012
4. Park et al. Can Res Treat 2011

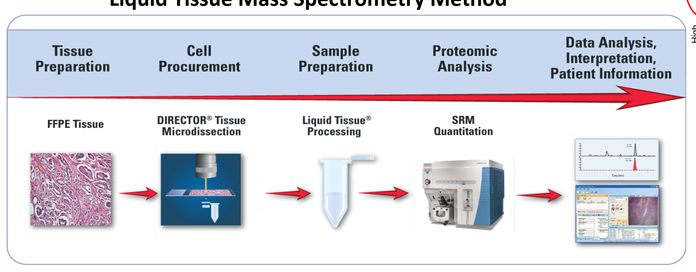


Methods

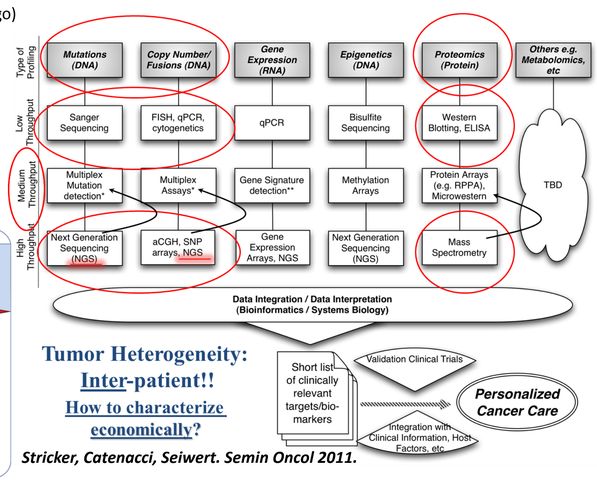
Cell Lines[1] were all obtained from ATCC, except MKN-45 (DSMZ) and Cat2 (University of Chicago)
FFPE (Formalin Fixed & Paraffin Embedded) **Cell line** clots were used for IHC and FISH
FFPE Tissues were obtained from the University of Chicago under an IRB approved protocol
IHC[1] (Immunohistochemistry) was performed as previously described.
FISH[1] (Fluorescence in situ hybridization) was performed as previously described.
NGS[2] (Nex-Gen Seq) was performed using the Foundation One Test (Foundation Medicine)
MS[3] (Mass Spectroscopy) was performed with OncoPlex Dx ('GEC plex')

1. Catenacci *et al. CBT* 2011. *2.* http://www.foundationone.com/
3. Hembrough *et al. J Clin Proteomics* 2012; http://oncoplexdx.com/

Liquid Tissue Mass Spectrometry Method



GEC cultured cells were washed, fixed with formalin, and subjected to Liquid Tissue® processing. FFPE tumor tissue blocks were cut on DIRECTOR® slides and processed using standard histological procedures. Tissues were laser microdissected on a Leica LMD-6000, collected in tubes and solubilized to tryptic peptides using Liquid Tissue® technology.

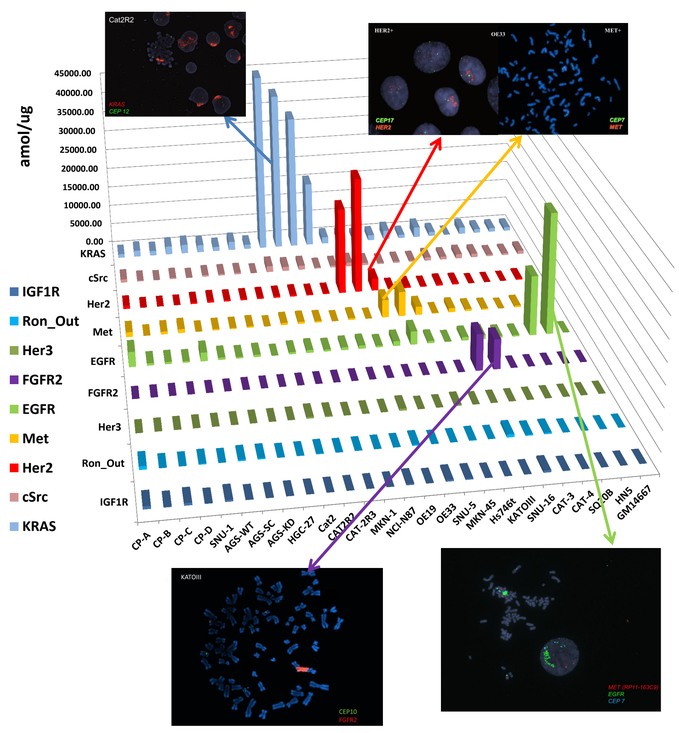


Tumor Heterogeneity: Inter-patient!!
How to characterize economically?

Stricker, Catenacci, Seiwert. Semin Oncol 2011.

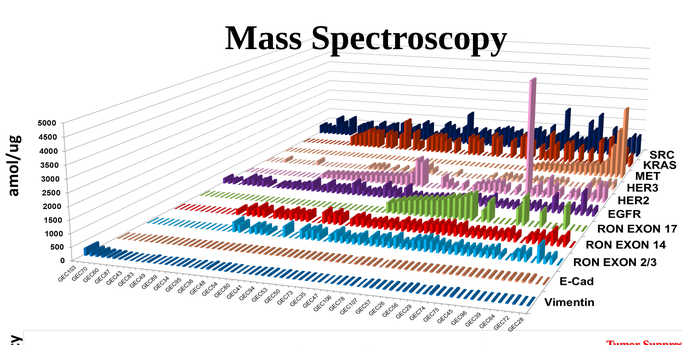
Catenacci et al. AACR-JCA 2013 Maui, HI. Abstr 141239
Catenacci et al. 24th EORTC NCI AACR 2012, Dublin, Ireland. Abstr 561
Hembrough et al. EACR 22nd Annual 2012, Barcelona, Spain. Abstr 820
Hembrough et al. AACR Mechanisms of Resistance 2012. San Diego, CA. Abstr A50

Inter-Cell Line Heterogeneity

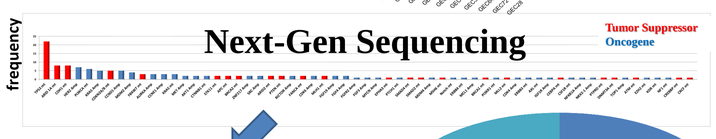


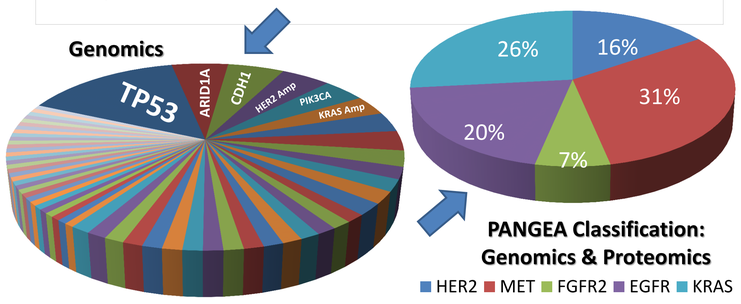
Inter-Patient Heterogeneity

Mass Spectroscopy



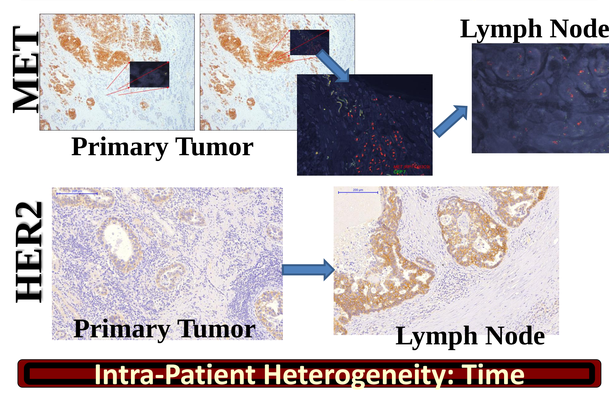
Next-Gen Sequencing



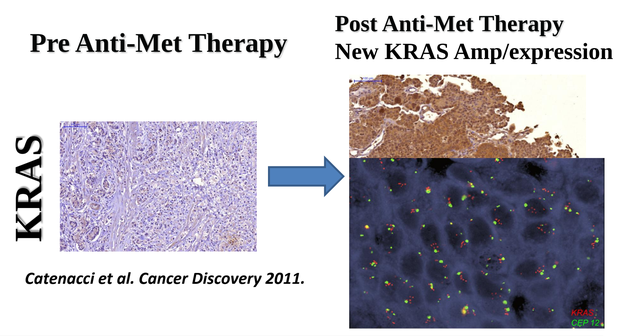


Patient	Oncogene	Tumor Suppressor
Metastatic (1-30) 1	HER2 Amp+	TP53 mt
2	HER2 Amp+	TP53 mt, ARID1A mt, FANCA mt
3	HER2 Amp+	FBXW7 mt, EPHA3 mt
4	HER2 Amp+, KRAS Amp+, PIK3R1 mt, CCND1 Amp+, CCNE1 Amp+, MCL1 Amp+, AKT1 Amp+	TP53 mt
5	MET Amp+, Notch mt	TP53 mt
6	KRAS Amp+	TP53 mt, CDKN2A mt, CDH1 Splice Site mt
7		ARID1A mt
8		TP53 mt
9	KRAS mt	FBXW7 mt, CDH1 Splice Site mt
10	KRAS mt, ERRB4 mt	BRCA2 mt, ARID1A mt
11	KRAS mt	
12	KRAS Amp+, RICTOR Amp+	TP53 mt
13	KRAS Amp+, CCND1 Amp+, CDK6 Amp+, AURKA Amp+, FGF19 Amp+, FGF4 Amp+ ZNF217 Amp+, NFKB1A Amp+, NKX2-1 Amp+	TP53 mt, STK11 loss
14	PIK3CA mt	PTCH1 mt, MLH1 mt, MSH6 mt
15	PIK3CA mt, CTNNB1 mt	TP53 mt, SMAD4 mt
16		TP53 mt, PTEN loss, SMAD4 mt
17	AKT1 Amp+	TP53 mt, CDH1 mt
18	MDM2 Amp+, AURKA Amp+, CTNNB1 mt, CSF1R mt	CDKN2A mt
19	CCND1 Amp+	TP53 mt
20	CCNE1 Amp+	TP53 mt
21	ZNF217 Amp+	TP53 mt, BRCA2 mt, STK11 mt
22		TP53 mt, BRCA1 mt, ARID1A mt
23		TP53 mt, APC mt
24		TP53 mt
25		TP53 mt
26		CDH1 mt
27	IGF1R Amp+	
28		CEBPA mt
29	MDM2 Amp+	APC mt, CDKN2A/B loss, PTPRD mt, DNMT3A
30	MET Amp+	
31	HER2 Amp+, SRC Amp+, TOP1 Amp+	
32	FGFR2 Amp+	TP53 mt, CDH1 mt
33	SRC Amp+, AURKA Amp+, CCND1 Amp+, CDK4 Amp+, RICTOR Amp+, MDM2 Amp+	CDKN2A/B Loss, ATM mt
34	HER2 Amp+, PIK3CA mt, CDK6 Amp+	TP53 mt, PTEN mt
35	MDM2 Amp+	
36	MYCN Amp+	TP53 mt, FANCA Loss
37	PIK3CA mt	
38		ARID1A mt, ARID2 mt, SMAD2 mt, MLL2 mt
39	HER2 Amp+, PIK3CA mt	TP53 mt
40		CDH1 mt, CDH1 Splice Site mt
41	CCND1 Amp+, EZH2 mt, FGF19 Amp+, FGF3 Amp+, FGF4 Amp+	
42		CDH1 Splice Site mt, CDKN2A mt, ARID1A mt, ARID2 mt
Resected (31-45) 43	PIK3CA mt, ERBB3 mt, AXL mt, KDR mt	NF1 mt, ARID1A mt, CREBBP mt CTCF mt, MLH1 mt
44		ARID1A mt
45	KRAS Amp+, CCNE1 Amp+, MDM4 Amp+	TP53 mt, FBXW7 mt, PTEN mt

Intra-Patient Heterogeneity: Space

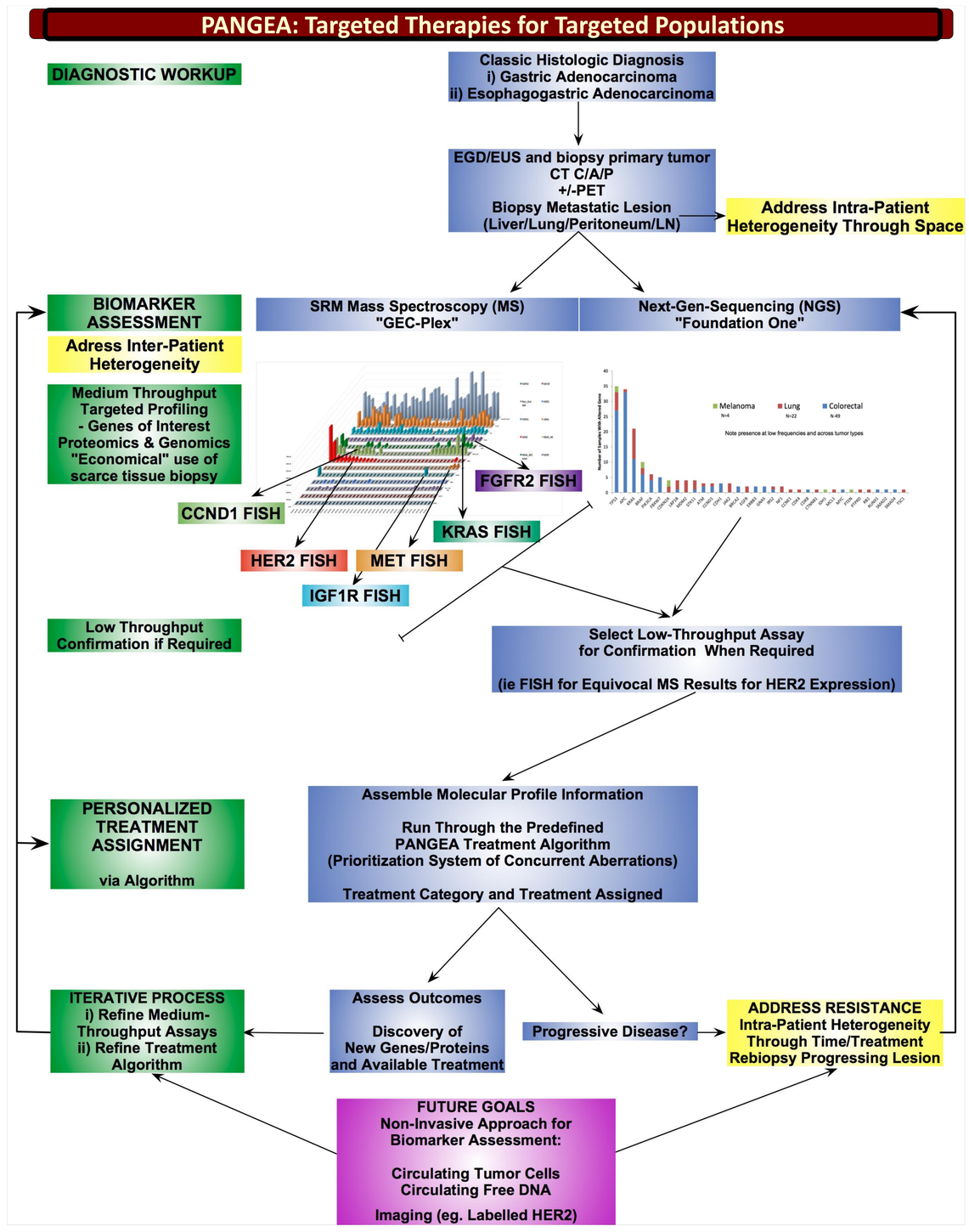


Intra-Patient Heterogeneity: Time

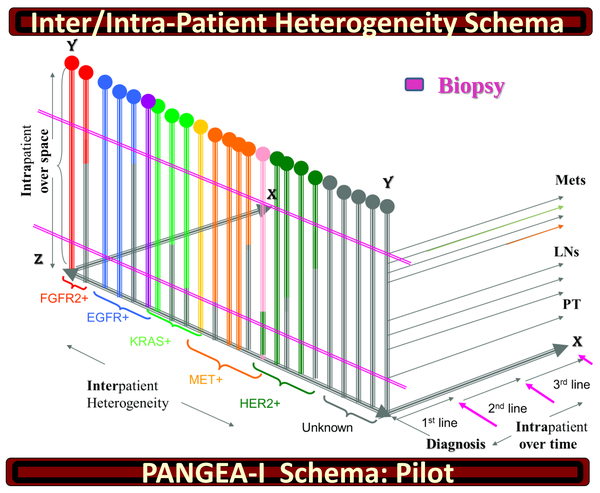


Catenacci et al. Cancer Discovery 2011.

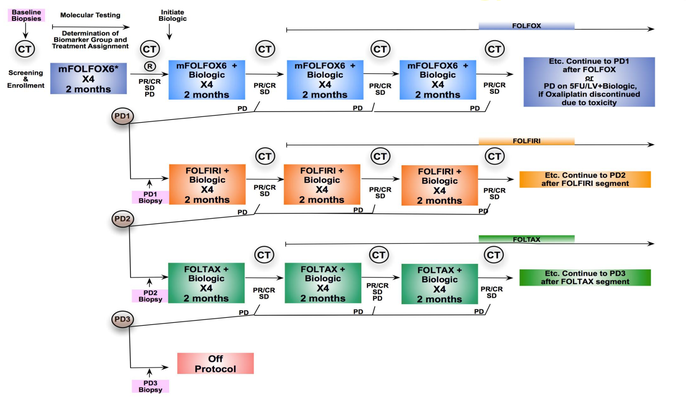
PANGEA: Targeted Therapies for Targeted Populations



Inter/Intra-Patient Heterogeneity Schema



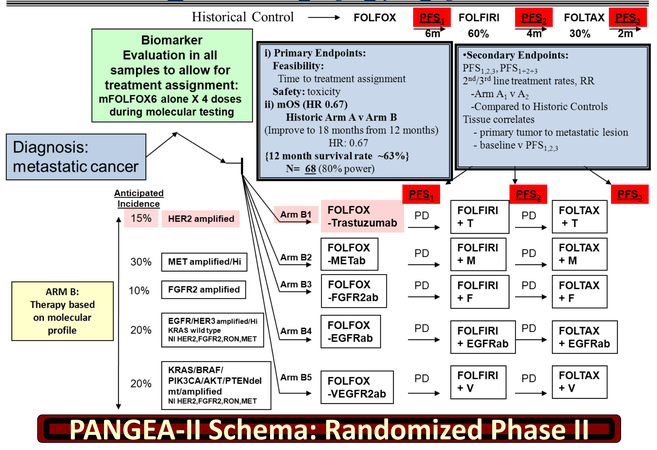
PANGEA Treatment Strategy



PANGEA-I Schema: Pilot

The PANGEA -MBBP Trial

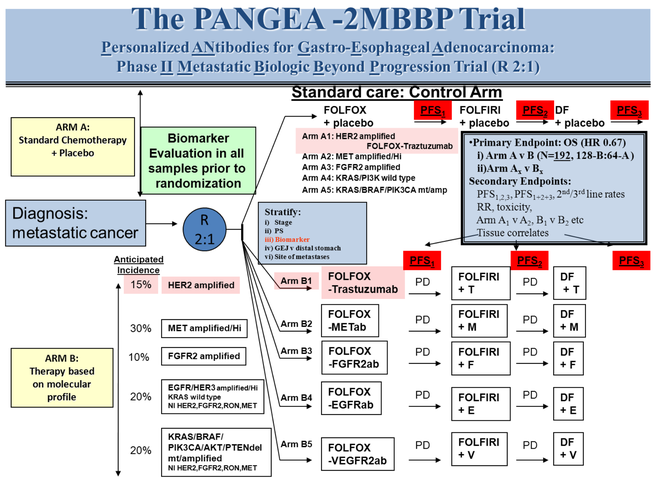
Personalized ANtibodies for Gastro-Esophageal Adenocarcinoma: A Metastatic Trial of Biologics Beyond Progression



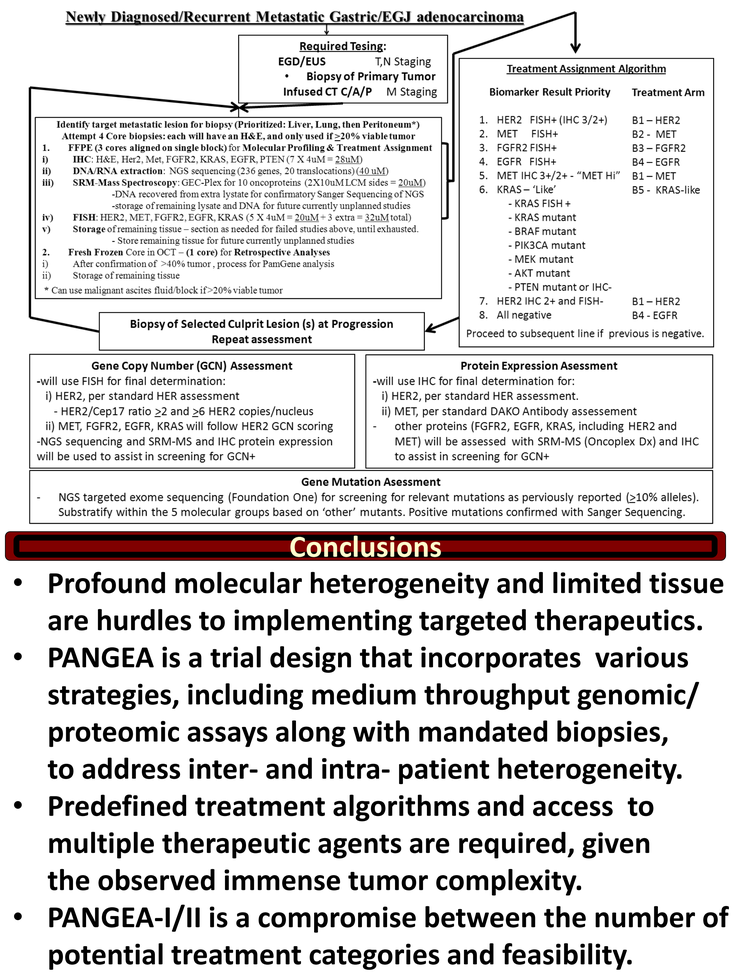
PANGEA-II Schema: Randomized Phase II

The PANGEA -2MBBP Trial

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



Biomarker & Treatment Assignment Algorithm



Conclusions

- **Profound molecular heterogeneity and limited tissue are hurdles to implementing targeted therapeutics.**
- **PANGEA is a trial design that incorporates various strategies, including medium throughput genomic/ proteomic assays along with mandated biopsies, to address inter- and intra- patient heterogeneity.**
- **Predefined treatment algorithms and access to multiple therapeutic agents are required, given the observed immense tumor complexity.**
- **PANGEA-I/II is a compromise between the number of potential treatment categories and feasibility.**
- **Future iterations may include more treatment groups**