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Supported by an Independent Educational Grant from BAYER

MEETING SUMMARY

ECC 2015, SEPTEMBER 25TH – 29TH 2015

BY PROF. DR. HANS PRENEN, LEUVEN, BELGIUM

Cancers of the Upper GI Tract

KU LEUVEN

RE-CLASSIFICATION OF GO CANCER THROUGH DISTINCT MOLECULAR PHENOTYPES

What disease are we trying to treat?

Histologic:

- Intestinal versus diffuse

Anatomic:

- GEJ versus body versus pylorus

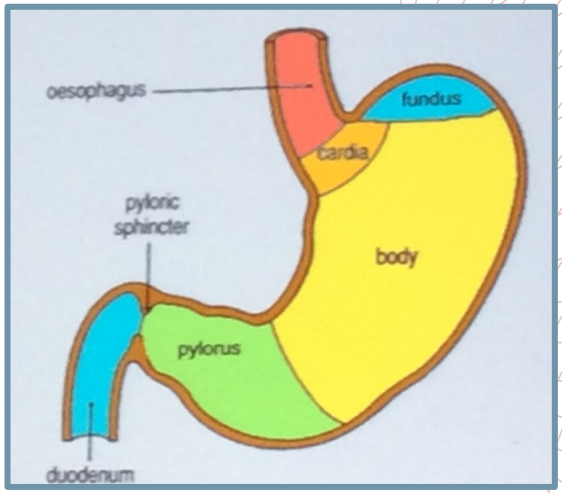
Geographic:

- East versus west

Molecular:

- MSI versus MSS ; HER2 +, ….

Dr A. Bass



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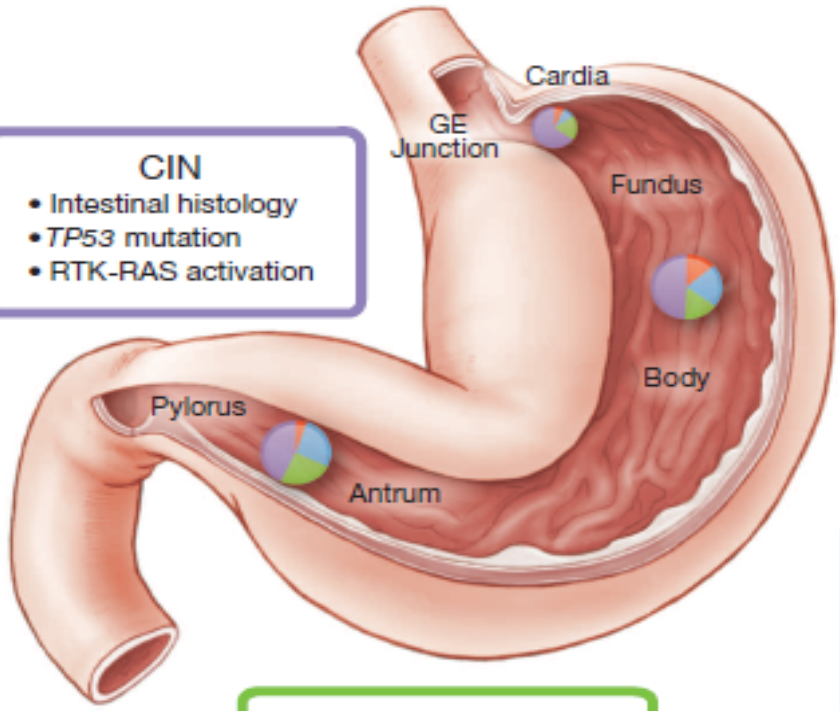
FOUR MOLECULAR CLASSES OF GASTRIC CANCER

50%



CIN
- Intestinal histology
- *TP53* mutation
- RTK-RAS activation

9%

EBV
- *PIK3CA* mutation
- *PD-L1/2* overexpression
- EBV-CIMP
- *CDKN2A* silencing
- Immune cell signalling

MSI
- Hypermutation
- Gastric-CIMP
- *MLH1* silencing
- Mitotic pathways

GS
- Diffuse histology
- *CDH1, RHOA* mutations
- *CLDN18–ARHGAP* fusion
- Cell adhesion

20%

22%

EBV, Epstein–Barr virus (red); MSI, microsatellite instability (blue), GS, genomically stable (green); CIN, chromosomal instability (light purple)

Nature 2014

COMPARISON OF EASTERN AND WESTERN GC STRATIFIED BY CIN

"Tumor subtype appears to be a stronger discriminator compared to geography"

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Schumacher et al, under review

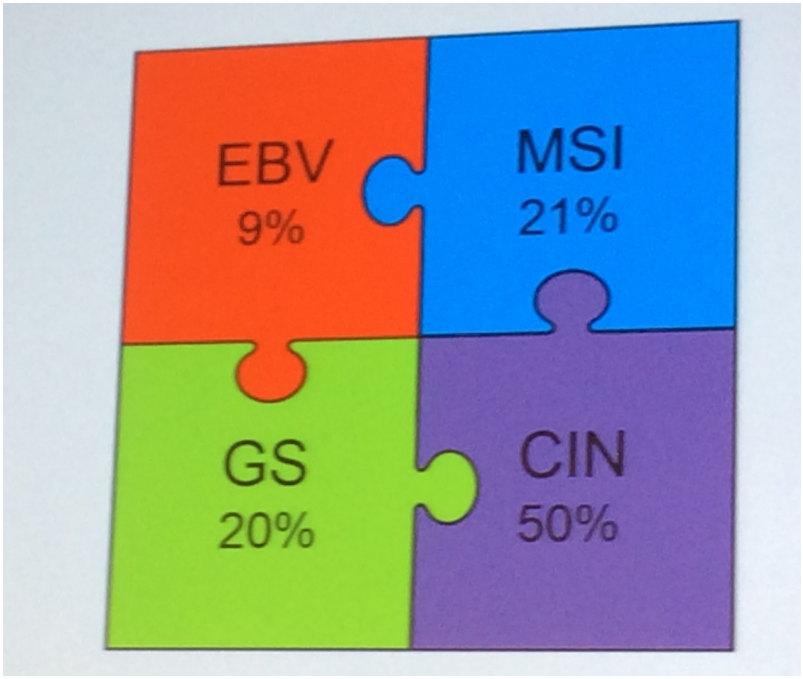
IMPLICATION FOR THERAPEUTIC EXPLOITATION

David Cunningham

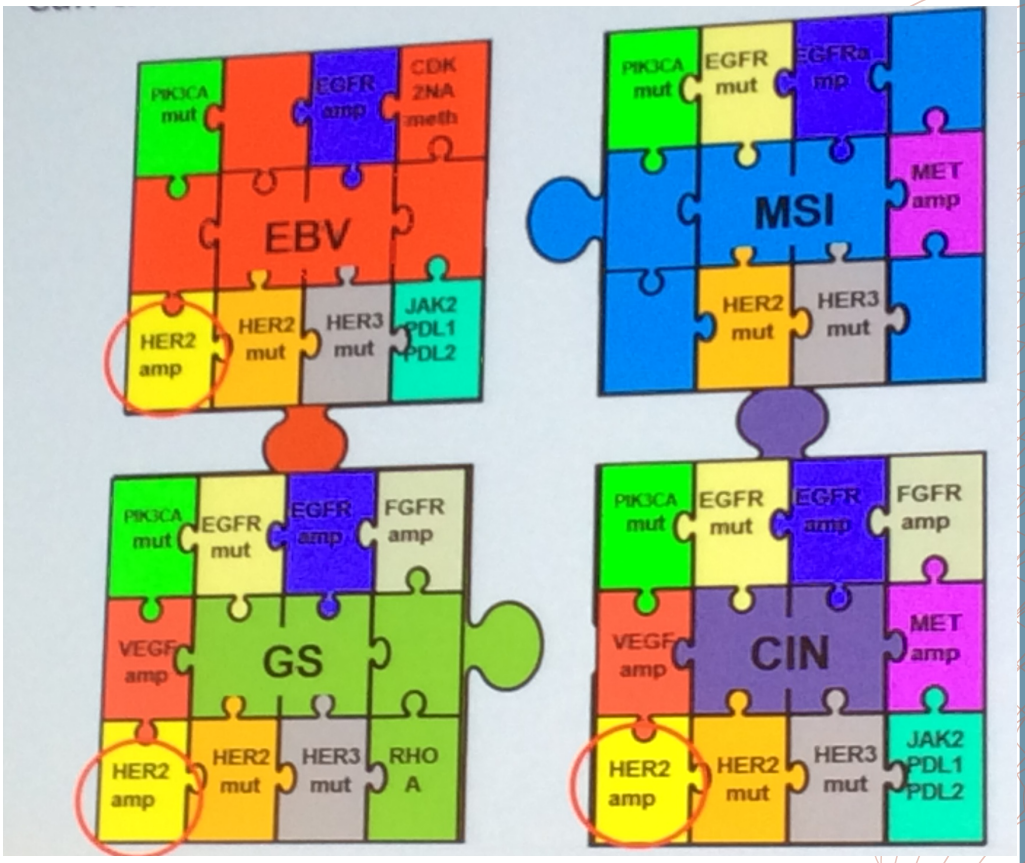
Caveats:

- Follow-up is short (<1y median) therefore limited prognostic utility
- Does not predict chemosensitivity or sensitivity to targeted therapy
- Proportion of EBV and MSI subgroups likely to be different in early versus late stage disease (as all tumors in TCGA were resected)

CAN TREATMENT BE TAILORED ACCORDING TO TCGA SUBTYPE?



This may be an oversimplification



TCGA does not predict for target “Enriched”

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Pathological response to neoadjuvant 5-FU, oxaliplatin and docetaxel (FLOT) versus epirubicin, cisplatin and 5-FU (ECF) in patients with locally advanced, resectable gastric/ esophagogastric junction (EGJ) cancer: Data from the phase II part of the FLOT4 phase III study of the AIO.

Claudia Pauligk, Andrea Tannapfel, Johannes Meiler, Kim Barbara Luley, Hans-Georg Kopp, Nils Homann, Ralf Dieter Hofheinz, Harald Schmalenberg, Stephan Probst, Georg Martin Haag, Matthias Egger, Dirk M. Behringer, Jan Stoehlmacher, Nicole Prasnikar, Andreas Block, Jörg Trojan, Gunnar Folprecht, Michael Pohl, Peter Schirmacher, Salah-Eddin Al-Batran

Late-Breaking Abstract ID: 36LBA

INTRODUCTION

- ECF/ECX: a standard of care in the perioperative setting for esophagogastric cancer since MAGIC trial published 2006
- 5-year survival <40%, not satisfactory!
- FLOT, a docetaxel-based triple-combination showed high rate of clinical and pathological remission in patients with esophagogastric cancer with an acceptable toxicity profile[1-5]
- Rates of complete pathological remission (pCR) of around 17-20%[2,5] with FLOT provided a rationale for the German randomized phase II/III FLOT4 trial, comparing FLOT with ECF(X)

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[1]Al-Batran 2008, [2]Homann 2012, [3]Al-Batran 2013, [4]Lorenzen 2013, [5]Schulz 2014

FLOT 4 STUDY DESIGN

- Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
- Medically and technically operable stages
- T2-4, every N, M0 or every T, N+, M0

STRATIFICATION

R

n=714

4xFLOT - OP - 4xFLOT

FLOT: docetaxel 50mg/m2, d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

3xECF(X) - OP - 3xECF(X)

ECF(X): Epirubicin 50 mg/m2, d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks

AIO

Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

Primary endpoint Phase II (n=300): rate of complete pathological remission (pCR)
Primary endpoint for phase III (n=714): OS, HR 0.76, power 80%, two sided p<0.05

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BASELINE CHARACTERISTICS

	ECF/ECX N=137		FLOT N=128		Total N=265	
	no.	%	no.	%	no.	%
Median Age	62	years	62	years	62	years
Male	100	73,0	102	79,7	202	76,2
Female	37	27,0	26	20,3	63	23,8
Primary						
Gastric	59	43,1	68	53,1	127	47,9
AEG I	35	25,5	32	25,0	67	25,3
AEG II	37	27,0	22	17,2	59	22,3
AEG III	6	4,4	6	4,7	12	4,5
T3/T4	110	80,3	104	81,3	214*	80,8
T1/T2	24	17,5	22	17,2	46*	17,4
N+	109	79,6	98	76,6	207*	78,1
N-	27	19,7	30	23,4	57*	21,5
Lauren Classification						
intestinal	60	43,8	52	40,6	112	42,3
diffuse	39	28,5	34	26,6	73	27,5
mixed/unknown	38	27,7	42	32,8	80	30,2

*Missing values: data for T or N stage not available.

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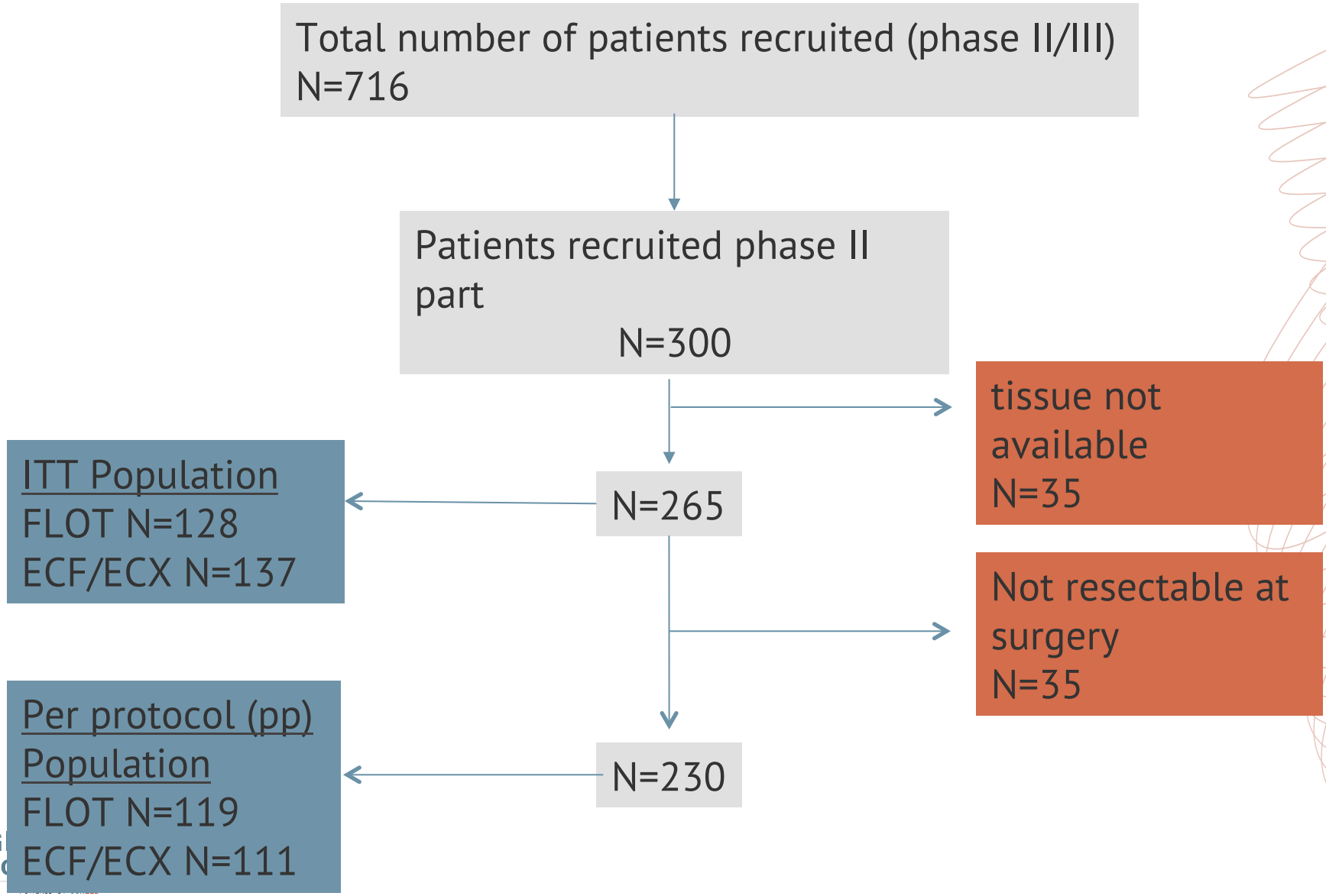
CONSORT DIAGRAM



PATHOLOGICAL REMISSION WITH ECF/ECX VS. FLOT – CENTRAL EVALUATION, ITT GROUP*

Pathological regression	ECF/ECX n(%) N=137		FLOT n(%) N=128		P-Value (2-sided)
Complete (pCR)	8	5,8	20	15,6	.015
Subtotal (pSR)	23	16,8	27	21,1	
pCR+pSR	31	22,6	47	36,7	.015
Partial (pPR)	28	20,4	23	18,0	
Minor (pMR)	44	32,1	45	35,2	
No response (pNR)	8	5,8	4	3,1	
Not resectable	26	19,0	9	7,0	

*primary Endpoint phase II

STO3 (ITT) 5.4%

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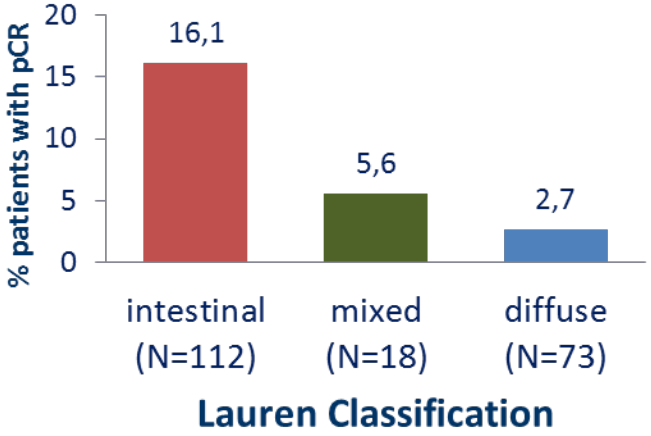
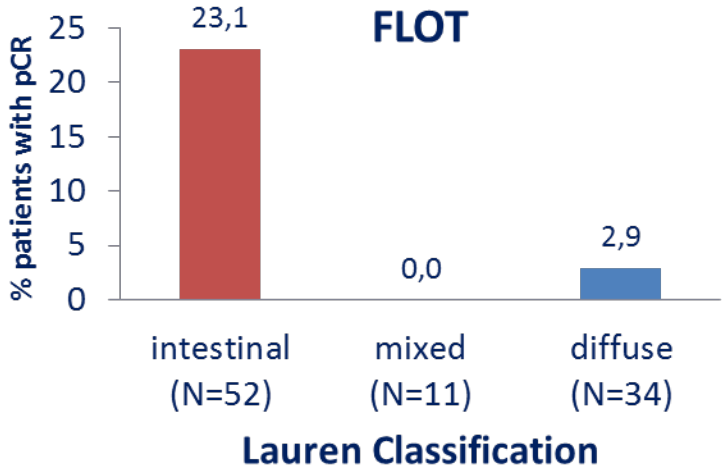
PATHOLOGICAL REMISSION WITH ECF/ECX VS. FLOT – CENTRAL EVALUATION, PP GROUP

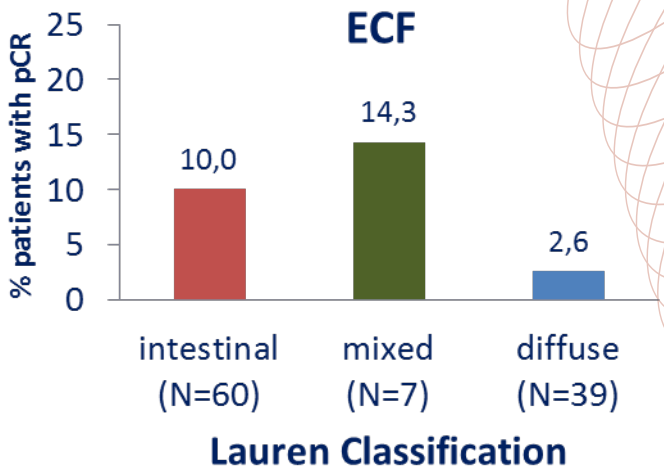
Pathological regression	ECF/ECX n(%) N=111		FLOT n(%) N=119		P-Value (2-sided)
Complete (pCR)	8	7,2	20	16,8	.028
Subtotal (pSR)	23	20,7	27	22,7	
pCR+pSR	31	27,9	47	39,5	.071
Partial (pPR)	28	25,2	23	19,3	
Minor (pMR)	44	39,6	45	37,8	
No response (pNR)	8	7,2	4	3,4	

STO3 8%

PCR IN CORRELATION WITH HISTOLOGY ACCORDING TO LAUREN







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CONCLUSION

- FLOT is associated with significantly higher rates of pCR than ECF(X)
- The results are in line with historical data from non-randomised studies
- Enrollment of the phase III trial is completed and survival results are expected in 2016/2017.