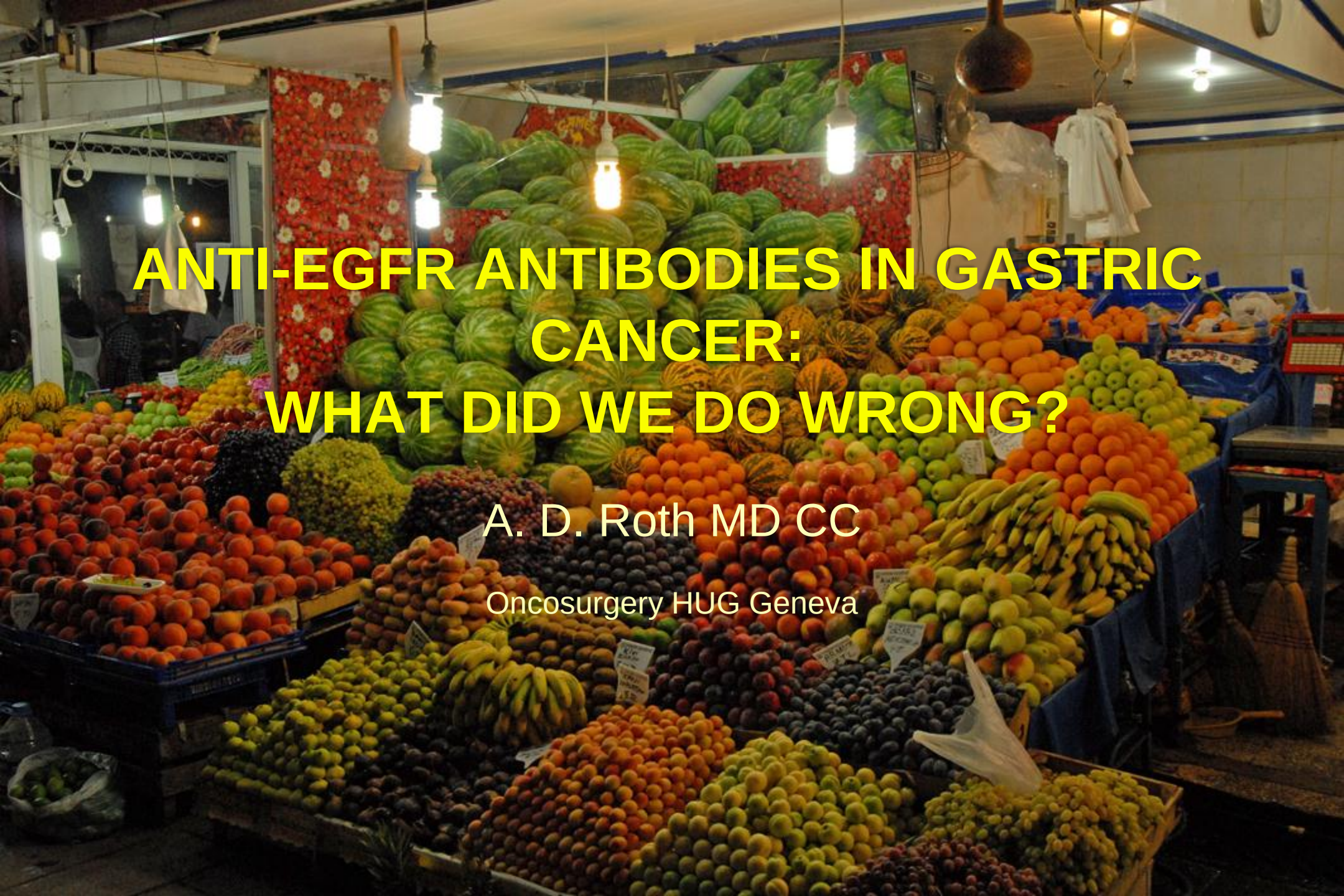


ANTI-EGFR ANTIBODIES IN GASTRIC CANCER: WHAT DID WE DO WRONG?

A. D. Roth MD CC

Oncosurgery HUG Geneva

Disclosures

- Honoraria
  - Merck KGaA

Expand disc. ESMO 2012

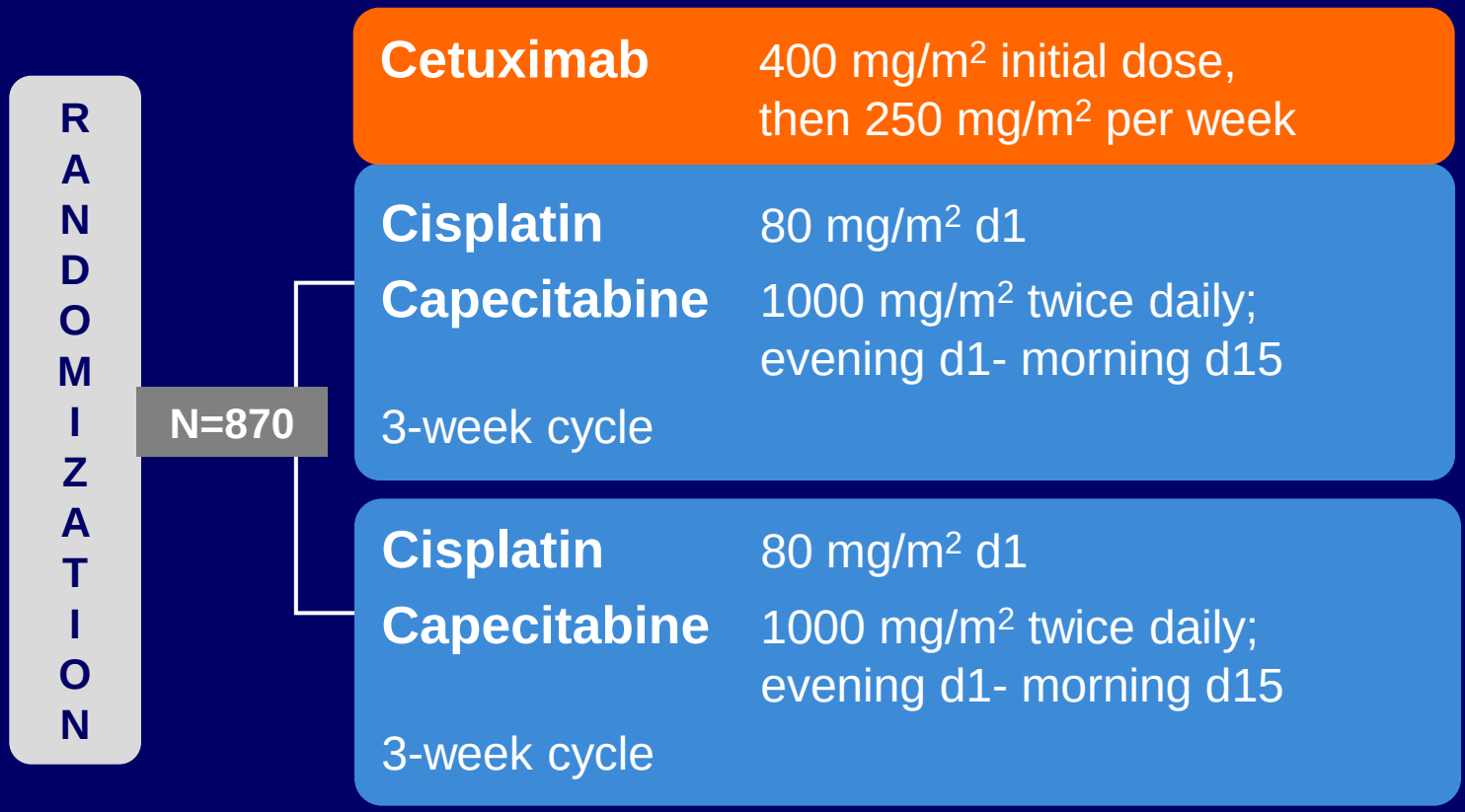
An apparently strong rationale.....

- EGFR pathway is important for tumor growth and metastases
  - Rates of EGFR over-expression vary in AGC
- Cetuximab
  - Chimeric IgG1 monoclonal antibody targeting EGFR
  - Mediates antibody-dependent cell-mediated cytotoxicity (ADCC)
  - Effective and safe in mCRC and SCCHN
  - Promising results in phase II studies in AGC[1-3]

EGFR, epidermal growth factor receptor;
mCRC, metastatic colorectal cancer;
SCCHN, squamous cell carcinoma of the head and neck

[1]Lordick F, et al. Br J Cancer 2010;102:500-5
[2]Moehler M, et al. Ann Oncol 2011;22:1358-66
[3]Pinto C, et al. Br J Cancer 2009;101:1261-68

Study design: it looks perfect!!



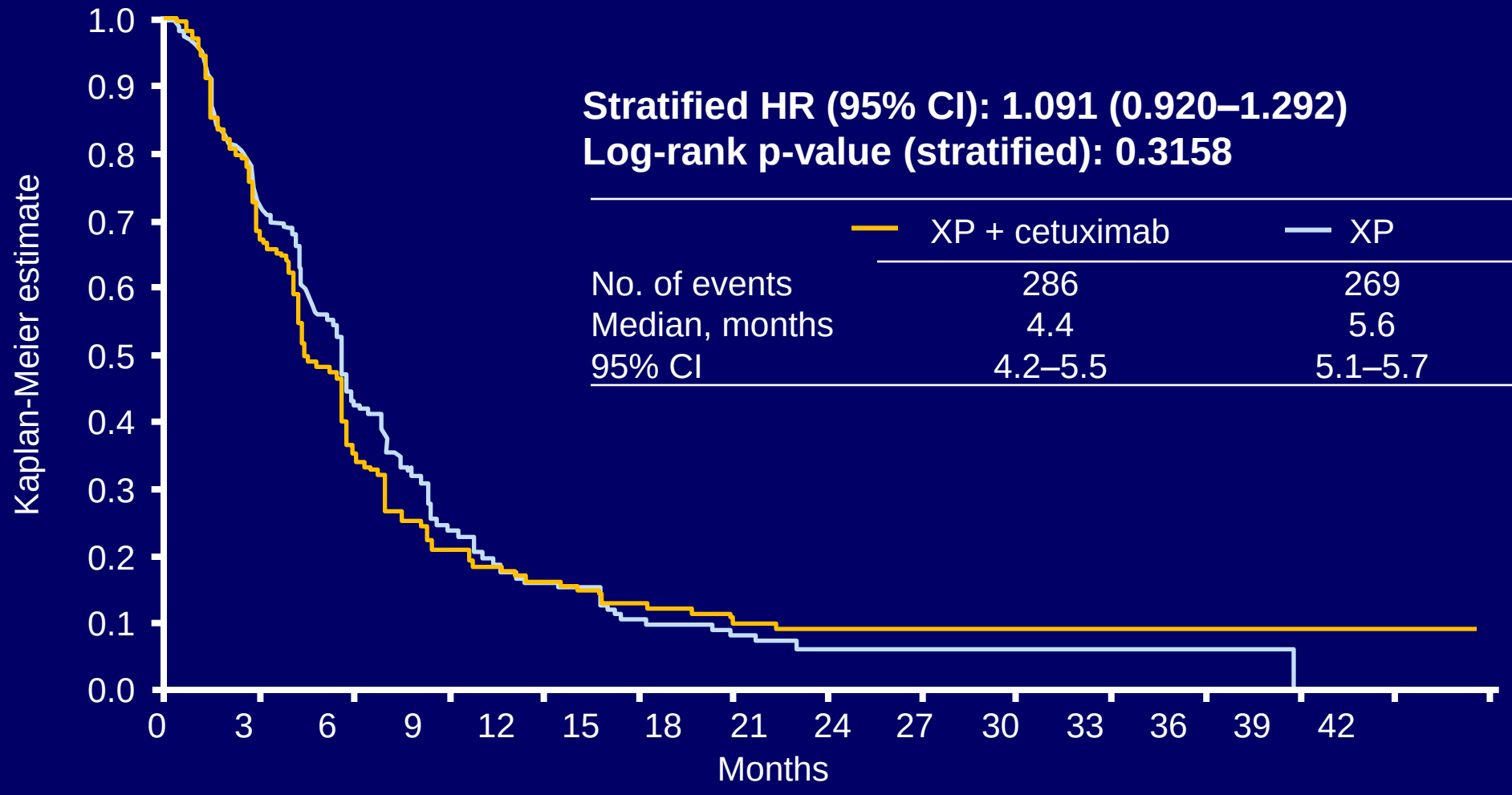
Study treatment until:

- Radiographically documented PD
- Unacceptable toxicity
- Withdrawal of consent

- Stratified by: disease status, prior oesophago-/gastrectomy, prior (neo-) adjuvant chemo (radio) therapy

PD, progressive disease

Primary endpoint: PFS (IRC)



Stratified HR (95% CI): 1.091 (0.920–1.292)
Log-rank p-value (stratified): 0.3158

	XP + cetuximab	XP
No. of events	286	269
Median, months	4.4	5.6
95% CI	4.2–5.5	5.1–5.7

XP + cetuximab	**455**	**233**	**94**	**44**	**30**	**20**	**14**	**8**	**4**	**4**	**3**	**3**	**1**	**1**	**0**
XP	**449**	**244**	**116**	**50**	**29**	**17**	**10**	**4**	**4**	**4**	**4**	**2**	**0**	**0**	**0**

HR, hazard ratio; IRC, independent review committee

Good Lord: another negative study to discuss at this congress…!

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A randomised multi-centre trial of epirubicin, oxaliplatin, and capecitabine plus panitumumab in advanced oesophagogastric cancer (REAL3)

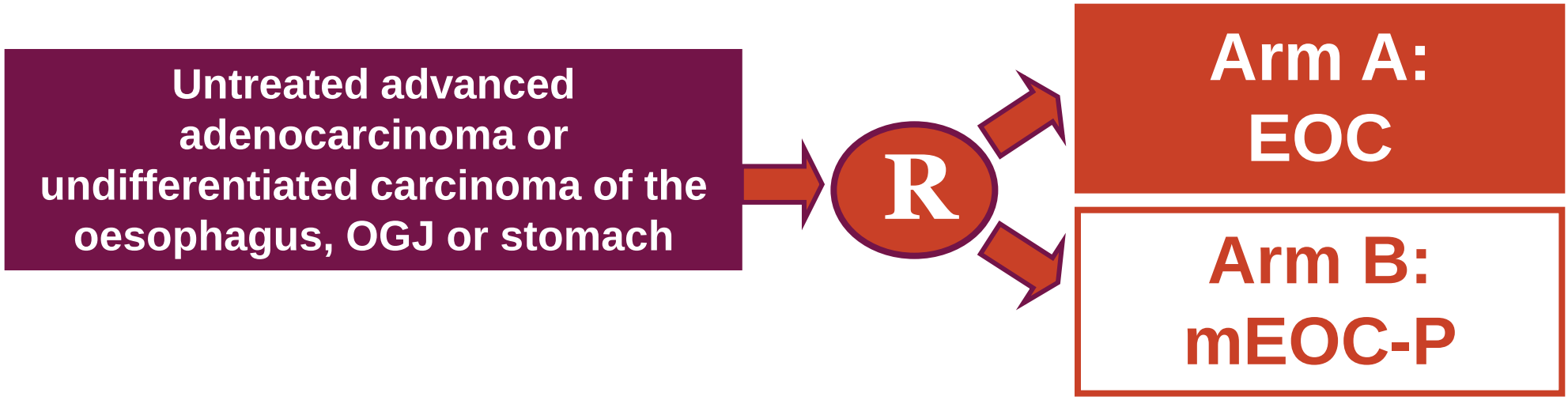
Dr T Waddell MBChB, MRCP

On behalf of the REAL-3 trial collaborators

T. Waddell, I. Chau, Y. Barbachano, D. Gonzalez-de-Castro, A. Wotherspoon, C. Saffery, G. Middleton, J. Wadsley, D. Ferry, W. Mansoor, T. Crosby, F. Coxon, D. Smith, J. Waters, T. Iveson, S. Falk, S. Slater, A. Okines, D. Cunningham

ASCO Annual '12 Meeting

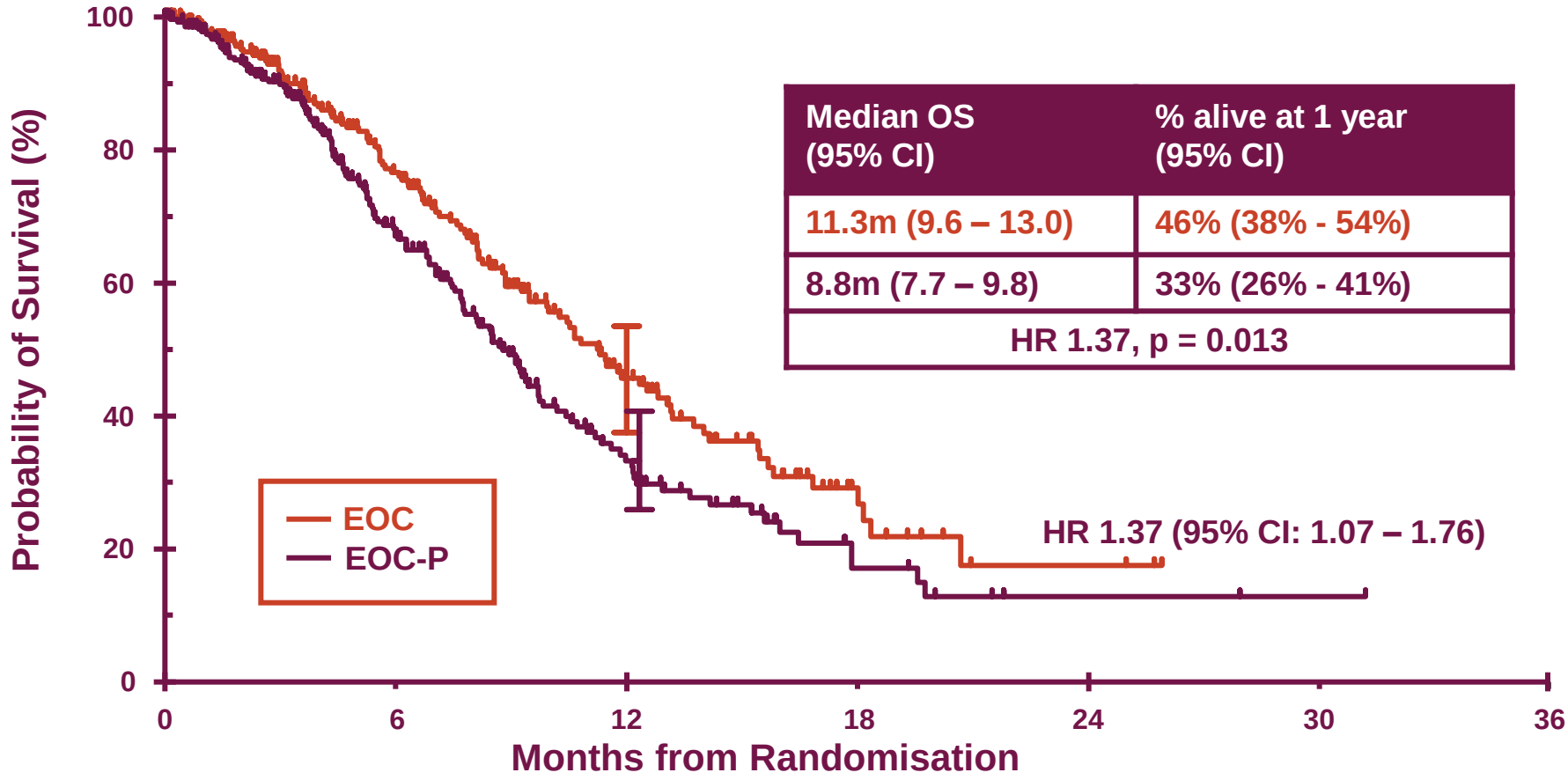
REAL3 Trial Design



- **EOC (Arm A):**
  - Epirubicin 50mg/m^2 IV D1
  - Oxaliplatin 130mg/m^2 IV D1
  - Capecitabine 1250mg/m^2/day PO in two divided doses D1-21
- **mEOC-P (Arm B)[1]:**
  - Epirubicin 50mg/m^2 IV D1
  - Oxaliplatin **100mg/m^2** IV D1
  - Capecitabine **1000mg/m^2/day** PO in two divided doses D1-21
  - Panitumumab 9mg/kg IV D1

1. Okines et al, JCO 2010

Primary Endpoint – OS



Median OS (95% CI)	% alive at 1 year (95% CI)
11.3m (9.6 – 13.0)	46% (38% - 54%)
8.8m (7.7 – 9.8)	33% (26% - 41%)
HR 1.37, p = 0.013	

Number at risk

EOC	275	49	3
EOC-P	278	38	2

Based on 251 OS events

Was the anti-EGFR arm too toxic?

Safety: Non-hematological AEs

	XP + cetuximab n=446		XP n=436	
Adverse events, %	**All**	**Grade 3/4**	**All**	**Grade 3/4**
Nausea	62	7	62	9
Decreased appetite	50	7	46	6
Vomiting	38	7	46	8
Rash	43	7	5	0
Fatigue	43	8	37	6
Diarrhea	40	8	25	4
Hand-foot syndrome	36	7	22	2
Hypomagnesemia	30	11	14	1
Asthenia	21	5	23	6
Hypokalemia	20	13	14	9

Relative dose intensity

Treatment, %	XP + cetuximab n=446	XP n=436
Cetuximab		
80 – <90%	22	
≥90%	60	
Cisplatin		
80 – <90%	28	25
≥90%	52	44
Capecitabine		
80 – <90%	23	20
≥90%	31	28

Dose Intensity

		EOC	mEOC-P
Median no. of cycles (n)		6	5
Dose intensity for cycles given (% of expected dose in each arm)	**Epirubicin**	89.9%	89.1%
	Oxaliplatin	89.9%	89.6%*
	Capecitabine	91.0%	86.9%*
	Panitumumab	-	88.1%
Dose reductions due to toxicity		36%	39%
Treatment cessation due to toxicity		18%	18%

* Not including protocol-specified baseline dose reductions

EXPAND first conclusions

- Well designed and conducted study
- No chemotherapy imbalance
- Negative results not explained by an increased toxicity in investigative arm
- Lack of molecular predictive marker for EGFR (in contrary to HER-2, TOGA trial)

Summary and conclusions

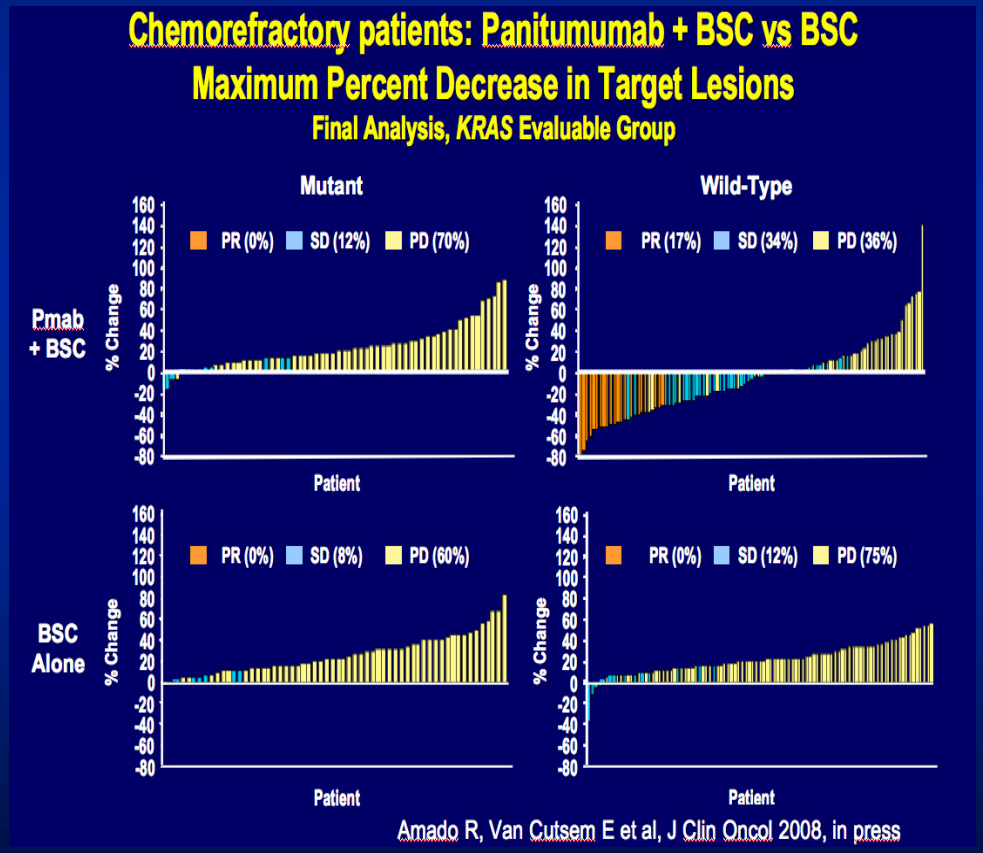
- No benefit from adding cetuximab to XP as first-line treatment for AGC in terms of
  - PFS (IRC)
  - OS
  - Best overall response (IRC)
- Consistent results across subgroups
- No new or unexpected safety findings but overall negative benefit/risk ratio for the experimental treatment
- **Further biomarker analysis is ongoing and will be reported at a later date**

A great opportunity for translational research!

- Expand = 904 patients (Real 3 = 553 pts)

- NOT the right setting to learn much more on anti-EGFRs and gastric cancer
  - Not a single drug (anti-EGFR) treatment trial
  - Small subgroups of interest at most => little stat power to detect them (the trial would have been positive otherwise)
  - Interference between potential prognostic value and predictivity

KRAS as negative predicting marker in colon cancer



- KRAS = 37% of colon cancer patients
- KRAS is not a prognostic marker in colon cancer
- In unstratified studies, there was already a strong signal

Expand disc. ESMO 2012

A great opportunity for translational research! (2)

- Expand = 904 patients (Real 3 = 553 pts)

- BUT a great opportunity for:
  - Testing in multivariate analysis for potential prognostic markers
  - Establish a subtyping classification of gastric cancer by genomic expression profiling

Prognostic markers in gastric cancer

- Search in Endnote™:
  - *title*: gastric cancer + prognostic marker: 34 entries
  - *abstract*: gastric cancer + prognostic marker: 388 entries

- We need a multivariate analysis including clinical staging in a large homogenous patient population:
  - To confirm or refute the most promising of them
  - To study their individual clinical relevance

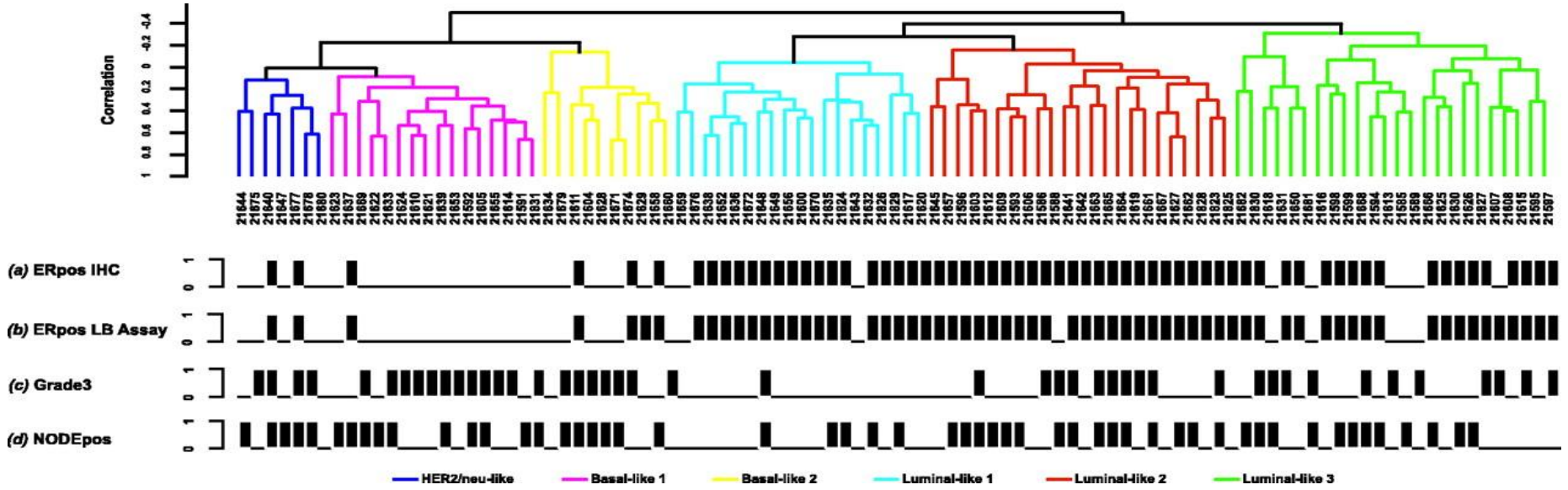
Multivariate Analysis for SAR in PETACC3 (N=392)

	HR (95% CI)	P-value
TTR (ER/LR)	**1.60 (1.23-2.09)**	**0.0005**
age	1.00 (0.99-1.01)	0.98
sex	1.24 (0.95-1.62)	0.11
Tumor Grade (G-34 / G-12)	**1.52 (1.02-2.25)**	**0.04**
stage (III versus II)	1.53 (1.00-2.36)	0.051
Tumor site (right/left)	**1.69 (1.29-2.21)**	**0.0002**
Treatment group	1.09 (0.84-1.39)	0.52
MSI (MSI-H / MSS)	**0.51 (0.28-0.95)**	**0.034**
Thymidilate synthetase	0.99 (0.68-1.44)	0.95
SMAD4	1.21 (0.91-1.60)	0.18
p53	0.96 (0.73-1.26)	0.76
hTERT	1.37 (0.96-1.96)	0.09
18qLOH	0.86 (0.60-1.24)	0.43
BRAF mut/wt	**3.61 (2.24-5.81)**	**1.24e-07**
KRAS mut/wt	1.13 (0.85-1.51)	0.40

A. Roth et al ASCO 2010

Expand disc. ESMO 2012

Dendrogram of 99 breast cancer specimens analyzed by hierarchical clustering analysis using 706 probe elements selected for the high variability across all tumors (see Materials and Methods).



Sotiriou C et al. PNAS 2003;100:10393-10398

Molecular biology in breast cancer: Intrinsic subtypes and signaling pathways

A

Molecular Subtype	Frequency	ER/PRg/HER2	CK5/6 EGFR	Genes of Proliferation	Characteristics genes	Histologic grade	TP53 mutations	Prognostic
Basal-like	10-20%	ER- PRg- HER2-	+	High	KRT5, CDH3, ID4, FABP7, KRT17, TRIM29, LAMC2	High	High	Bad
HER2-enriched	10-15%	ER- PRG- HER2+	+/-	High	ERBB2, GRB7	High	High	Bad
Normal breast-like	5-10%	ER-/+ HER2-	+	Low	PTN, CD36, FABP4, AQP7, ITGA7	Low	Low	Intermediate
Luminal A	50-60%	ER+ PRg+ HER2-	-	Low	ESR1, GATA3, KRT8, KRT18, XBP1, FOXA1, TFF3, CCND1, LIV1	Low	Low	Excelent
Luminal B	10-20%	ER+/- PRg+/- HER2-/+	-	High	ESR1, GATA3, KRT8, KRT18, XBP1, FOXA1, TFF3, SQLE, LAPTM4B	Intermediate /High	Intermediate	Intermediate /Bad
Claudin-low	12-14%	ER- PRg- HER2-	+/-	High	CD44, SNAI3	High	High	Bad

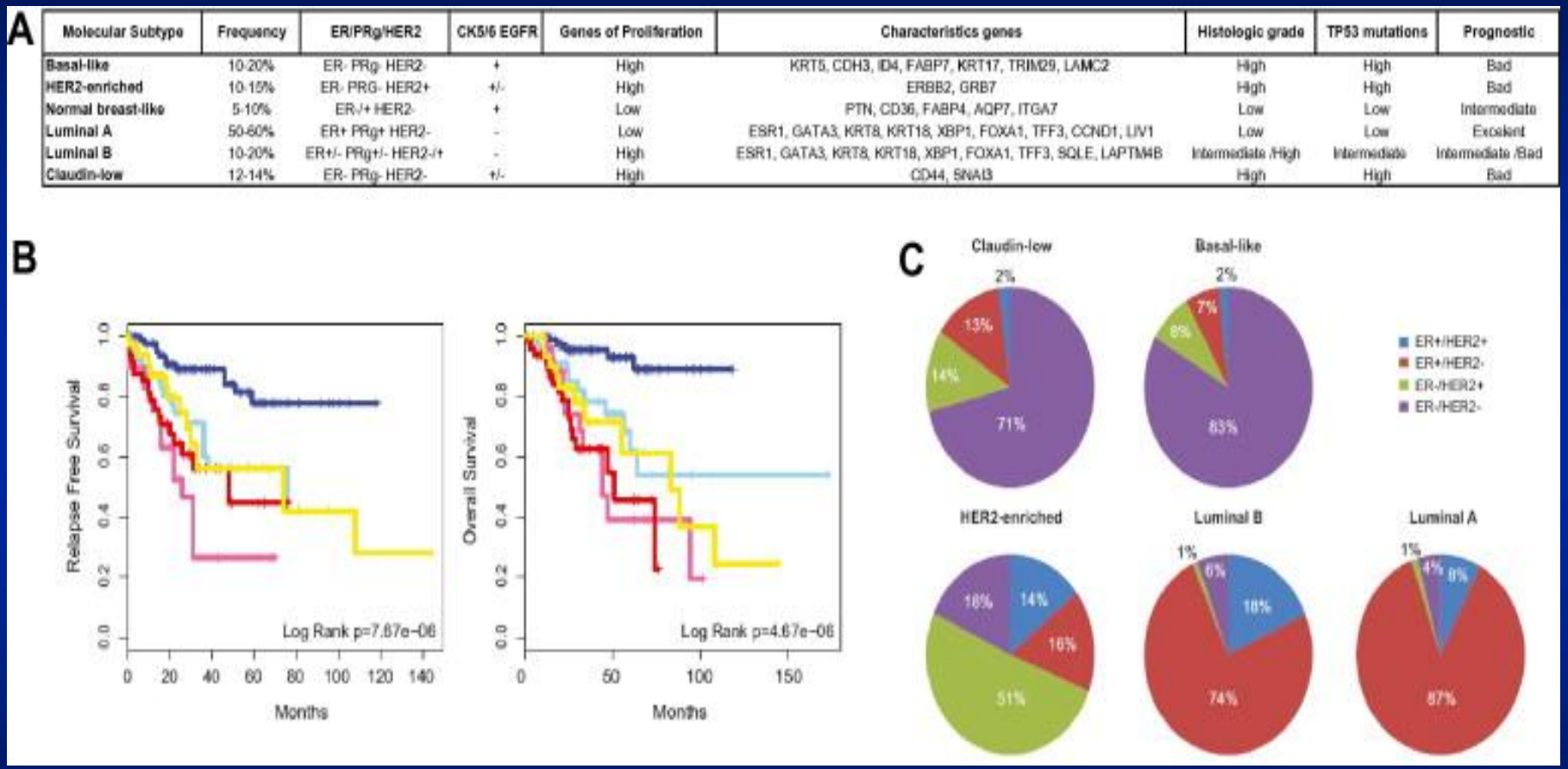
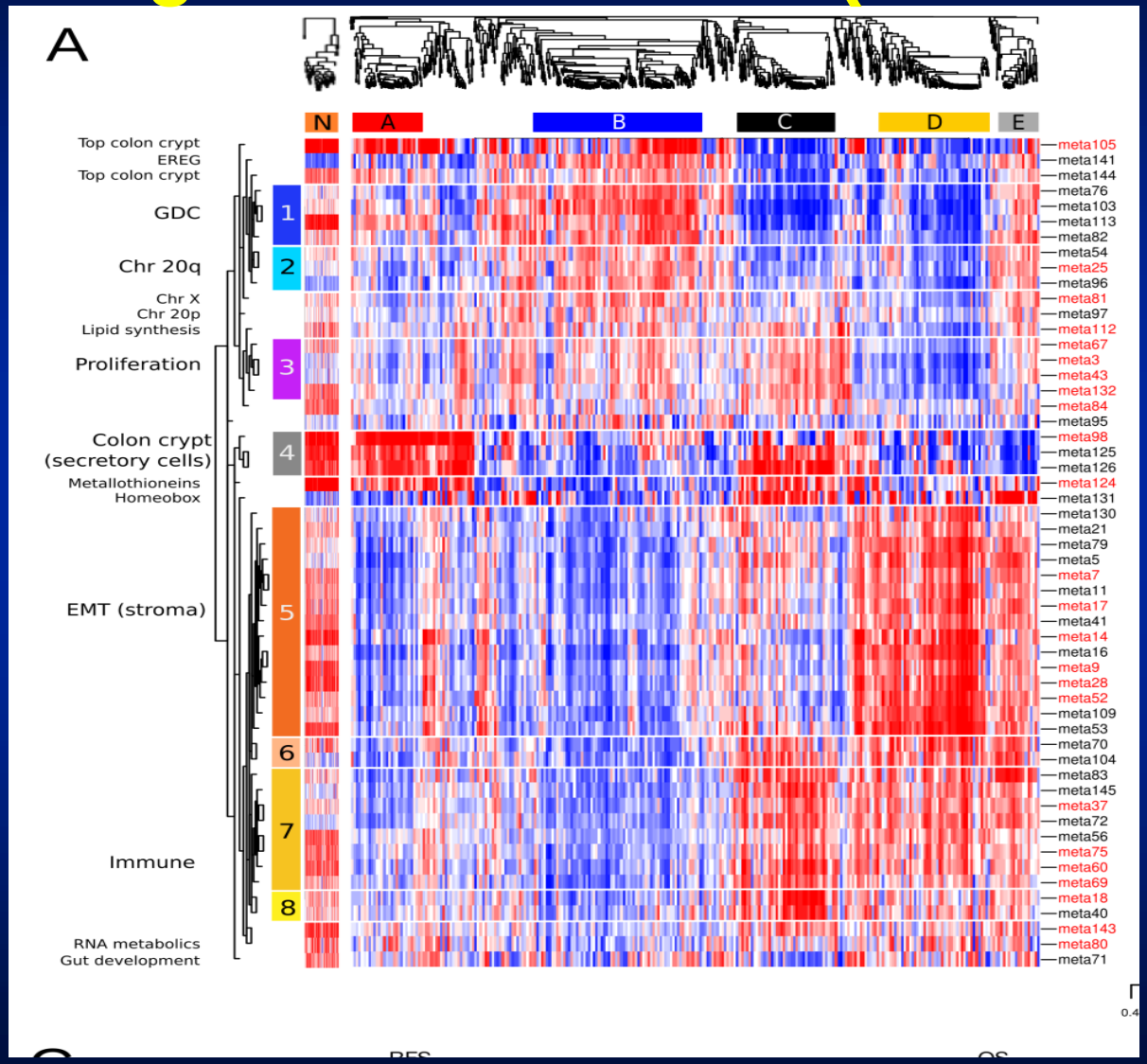


Fig. 1 (A) Features of molecular subtypes of breast cancer. (B) Kaplan?Meier curves of disease-free survival and overall survival based on UNC337 database. Dark blue, luminal A; light blue, luminal B; red, basal-like; pink, HER2-enriched; yellow, Claudin low.

P. Eroles, Cancer Treatment Reviews Volume 38, Issue 6 2012 698 - 707

Expand disc. ESMO 2012

Subtyping by genomic expression profiling of colon cancer (PETACC 3)



E. Budinska et al, ASCO 2012

Expand disc. ESMO 2012

Subtype summary

A – *normal -like epithelial*: KRAS, differentiated, no CSC markers, Wnt down, good OS and RFS

B – *proliferative epithelial*: differentiated, but lost secretory cells, proliferative, 20q genes up, Wnt active, MSS, nonBRAF, non-mucinous, good OS, RFS, SAR

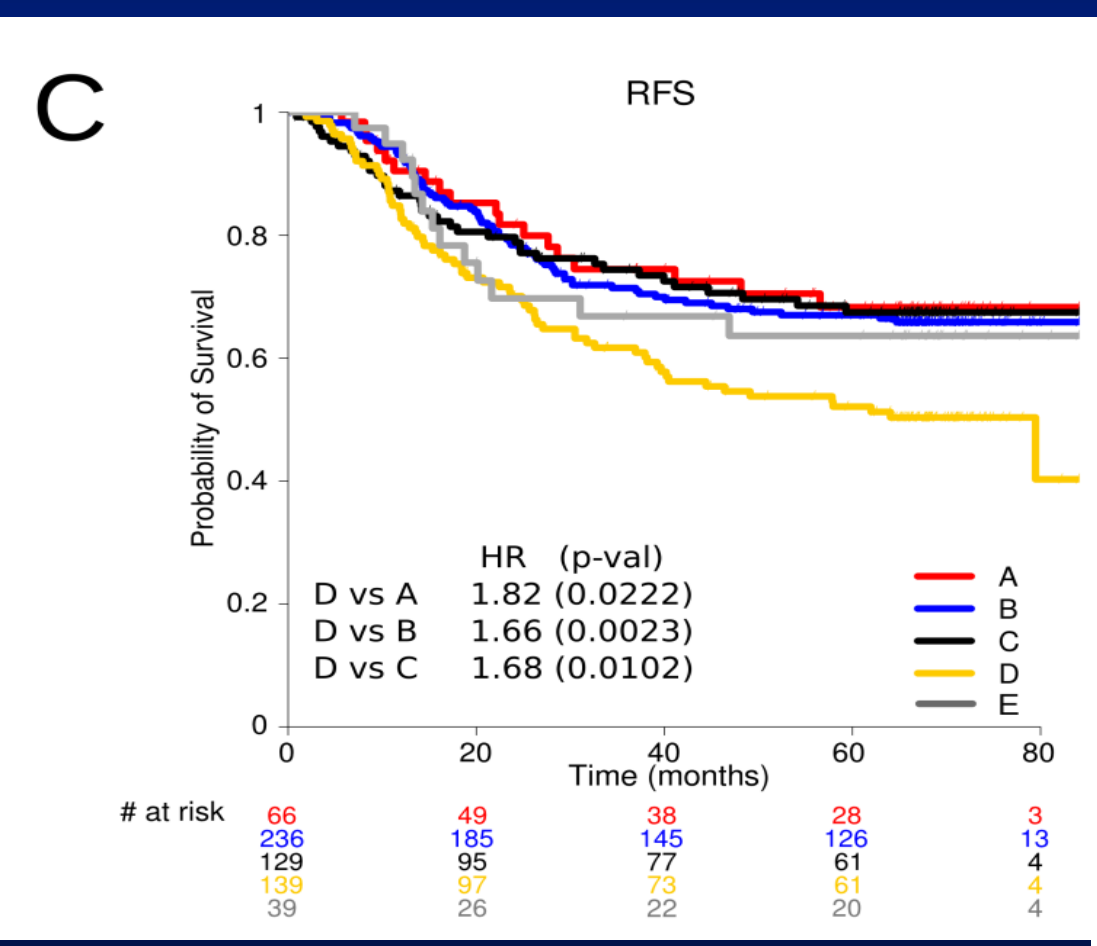
C – *CIMP-H like*: undifferentiated carcinomas, MSI, BRAF, mucinous, right, less frequently p53 mutated, enriched in females, proliferative, immune, CIMP+, the shortest SAR, poor OS

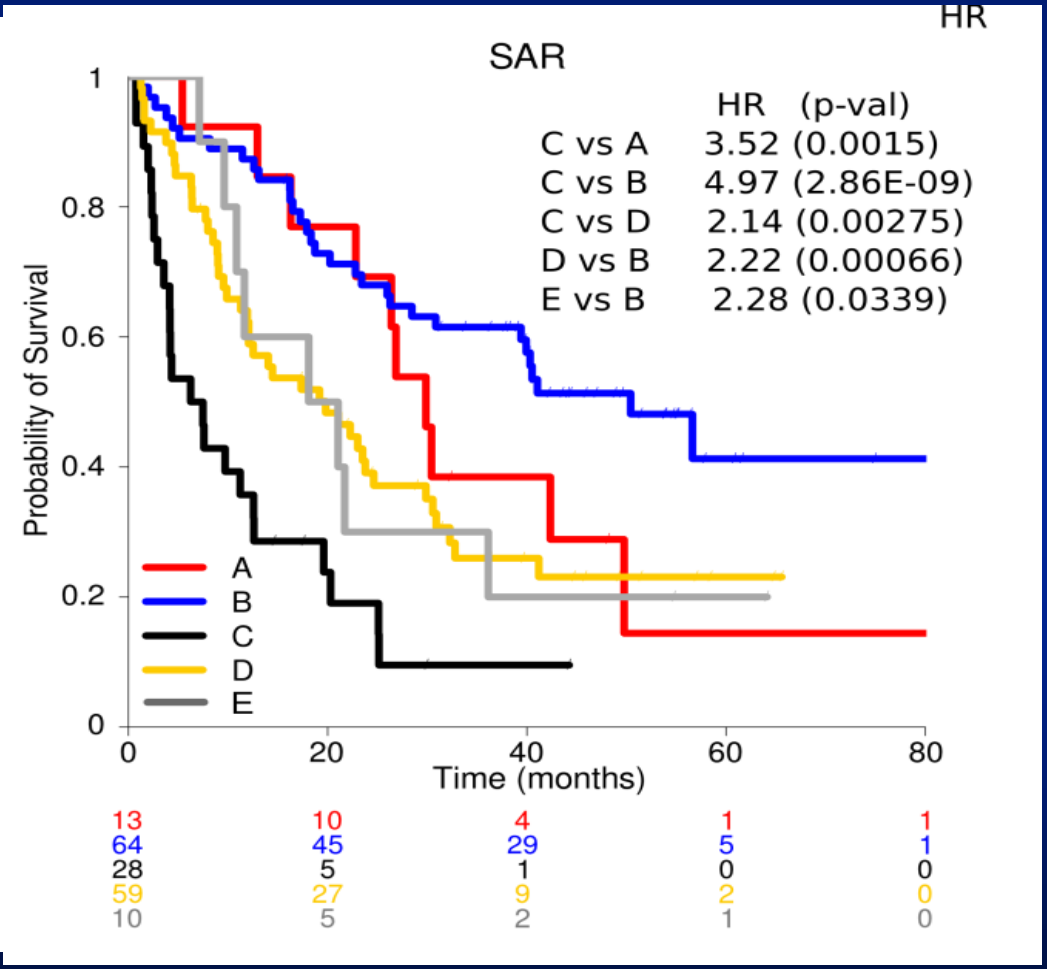
D – *mesenchymal*: no proliferation, high CSC markers, Wnt inactive, active EMT, the shortest RFS, poor OS and SAR

E – *intermediate*: MSS, nonBRAF, non mucinous, left, CSC markers, EMT, proliferation, differentiation, p53 enriched

E. Budinska et al, ASCO 2012

Colon Cancer Subtypes and Survival





E. Budinska et al, ASCO 2012

Expand disc. ESMO 2012

Genomic expression based subtyping of gastric cancer

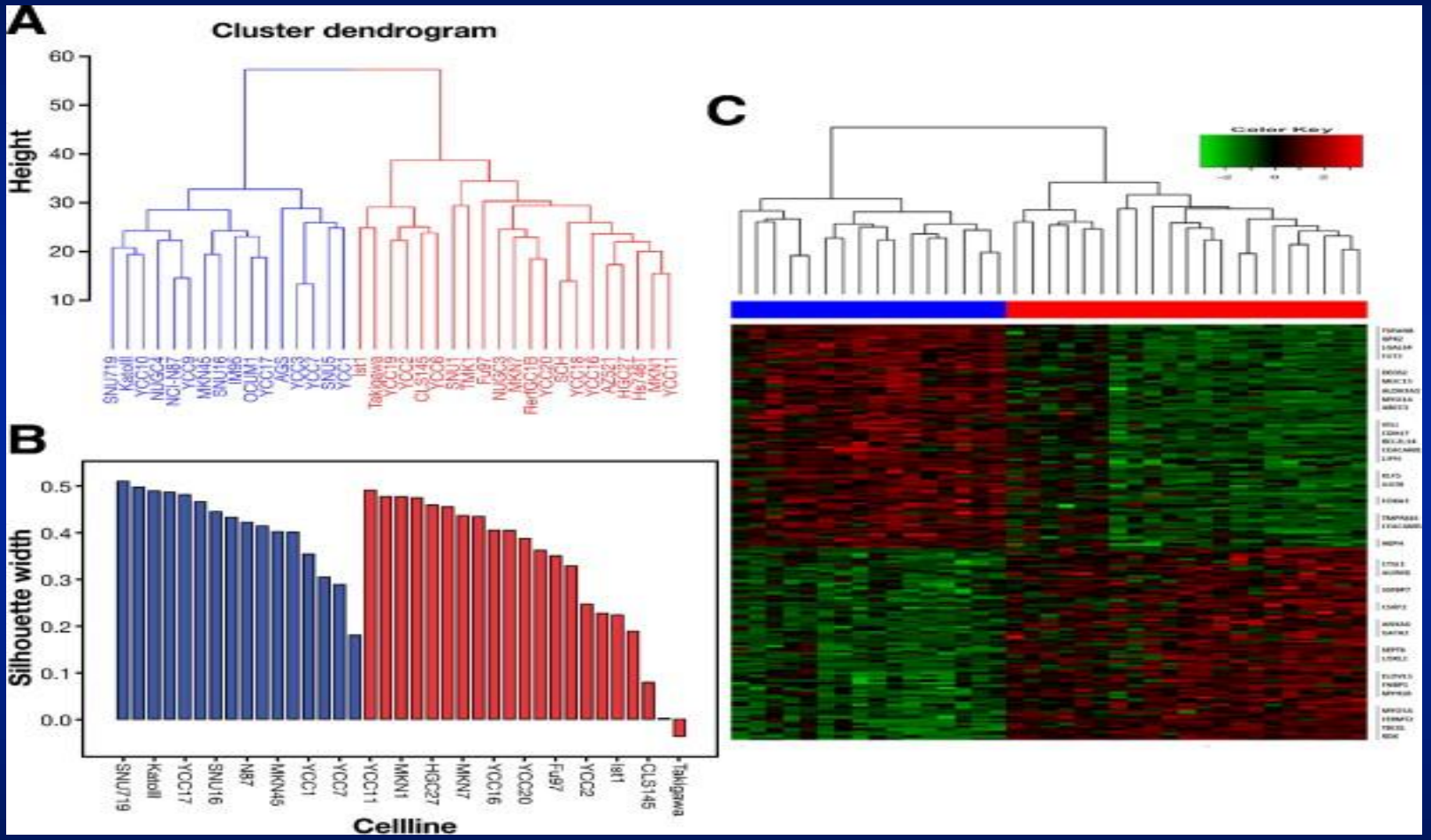


Figure 1 Unsupervised clustering of GC cell lines reveals 2 major intrinsic subtypes.

Iain Beehuat Tan Gastroenterology Volume 141, Issue 2 2011 476 - 485.e11

Expand disc. ESMO 2012

EXPAND IS MOST SUITABLE FOR TR BECAUSE:

- It is a large study in metastic gastic cancer
- It has an homogenous patient population
- It has a clinical data base of high quality
- Tumor material is readily available
- Patients have given their consent

WE HAVE MORAL OBLIGATION!