
GI
connect
POWERED BY COR2ED

WHAT IS THE RELEVANCE OF MOLECULAR SUBTYPES IN GI TUMORS?

Prof. Sebastian Stintzing
University Hospital Munich
Germany

March 2018

DISCLAIMER

GI connect
POWERED BY COR2ED

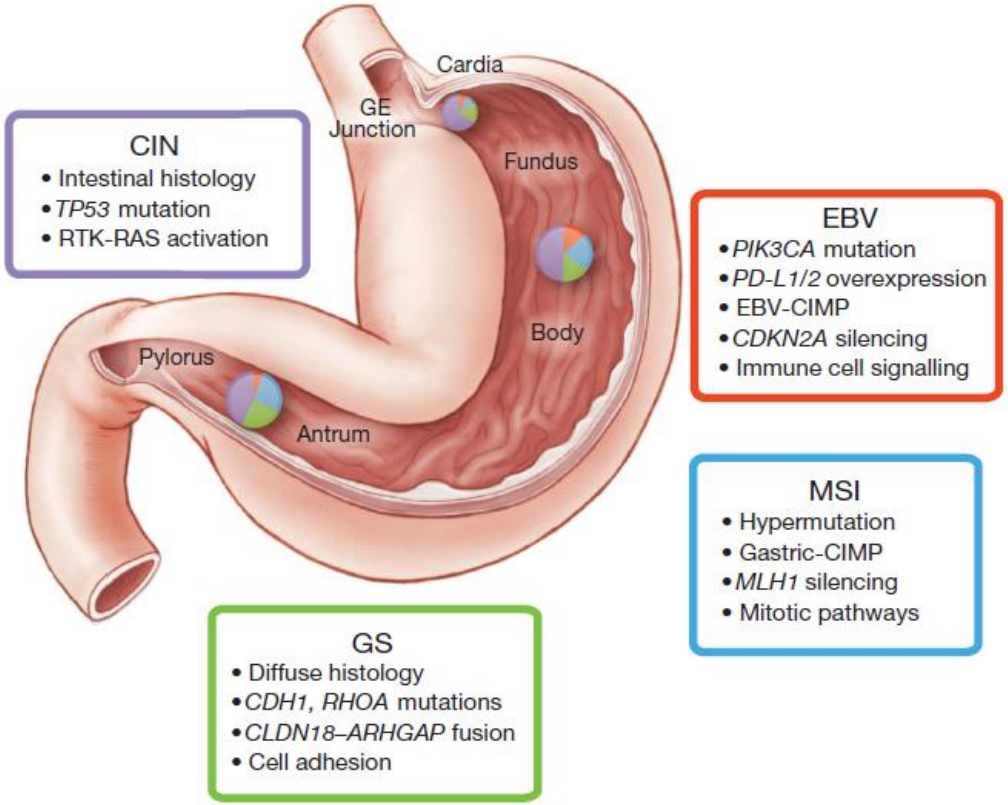
Please note:

The views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author's academic institution or the rest of the GI CONNECT group

TCGA RESEARCHERS IDENTIFY FOUR SUBTYPES OF STOMACH CANCER

GI connect
POWERED BY COR2ED

GENOMIC SUBTYPES OF GASTRIC CANCER

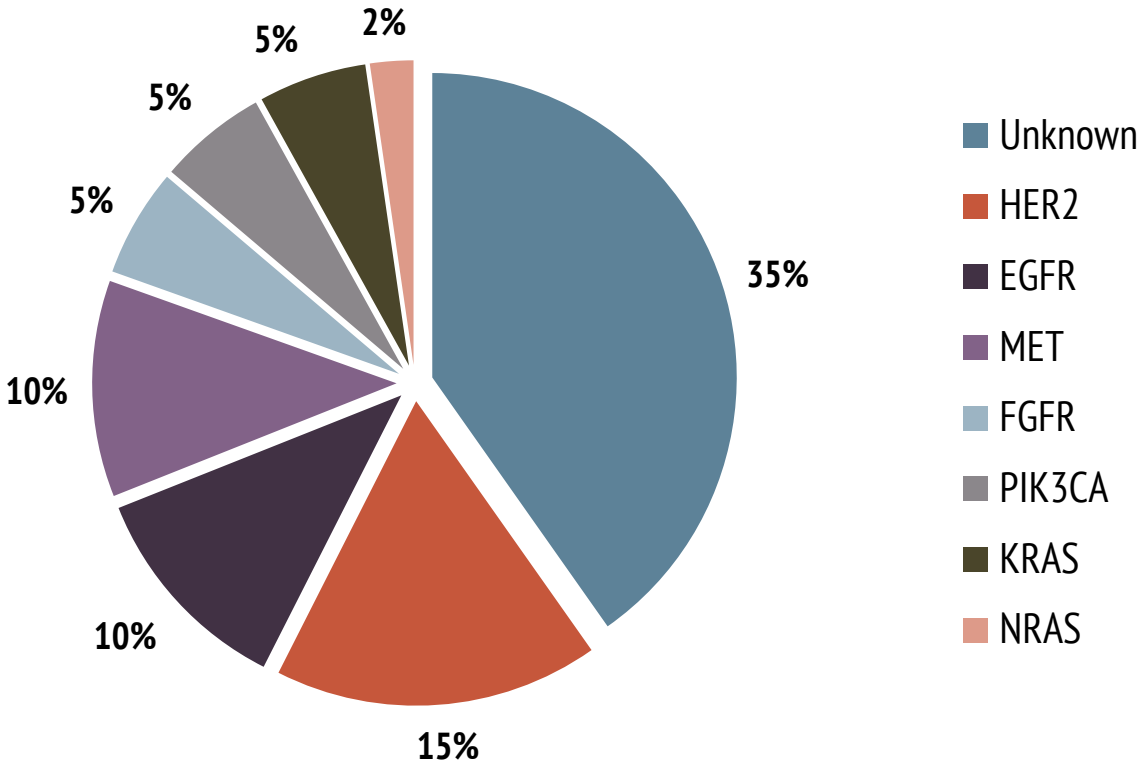


- 9% EBV positive
- 22% MSI
- 20% genomically stable tumors
- 50% chromosomally unstable tumors

TCGA Nature 2014; 513(7517): 202–9

ARHGAP, Rho GTPase activating proteins; CDH1, cadherin-1; CDKN2A, cyclin-dependent kinase Inhibitor 2A; CIMP, CpG island methylator phenotype; CIN, chromosomal instability; CLDN18, Claudin-18; EBV, Epstein-Barr virus; GE, gastroesophageal; GS, genomically stable; MLH1, MutL homolog 1; MSI, microsatellite instability; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit A; PD-L1/2, programmed death receptor ligand 1/2; RHOA, Ras homolog gene family member A; RTK-RAS, receptor tyrosine kinase Ras; TCGA, The Cancer Genome Atlas; TP53, tumor protein p53.

GASTRIC CANCER: ACTIONABLE MOLECULAR SUBTYPES



- All but HER2 have failed to change clinical practice
- HER2 positive gastric cancer which should be treated with trastuzumab (ToGa trial)

Yamada Y. Chin Clin Oncol. 2013; 2(1): 5.

EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, KRAS proto-oncogene, GTPase; MET, MET tyrosine kinase receptor; NRAS; NRAS proto-oncogene, GTPase; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit alpha; ToGa trial, Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer.

CLINICAL RELEVANCE OF SUBTYPES?

GI connect
POWERED BY COR2ED

- TCGA subtypes:
  - **MSI** may be treated with immune-checkpoint inhibitors (FDA approval)[1]
  - Others have no relevance (so far)

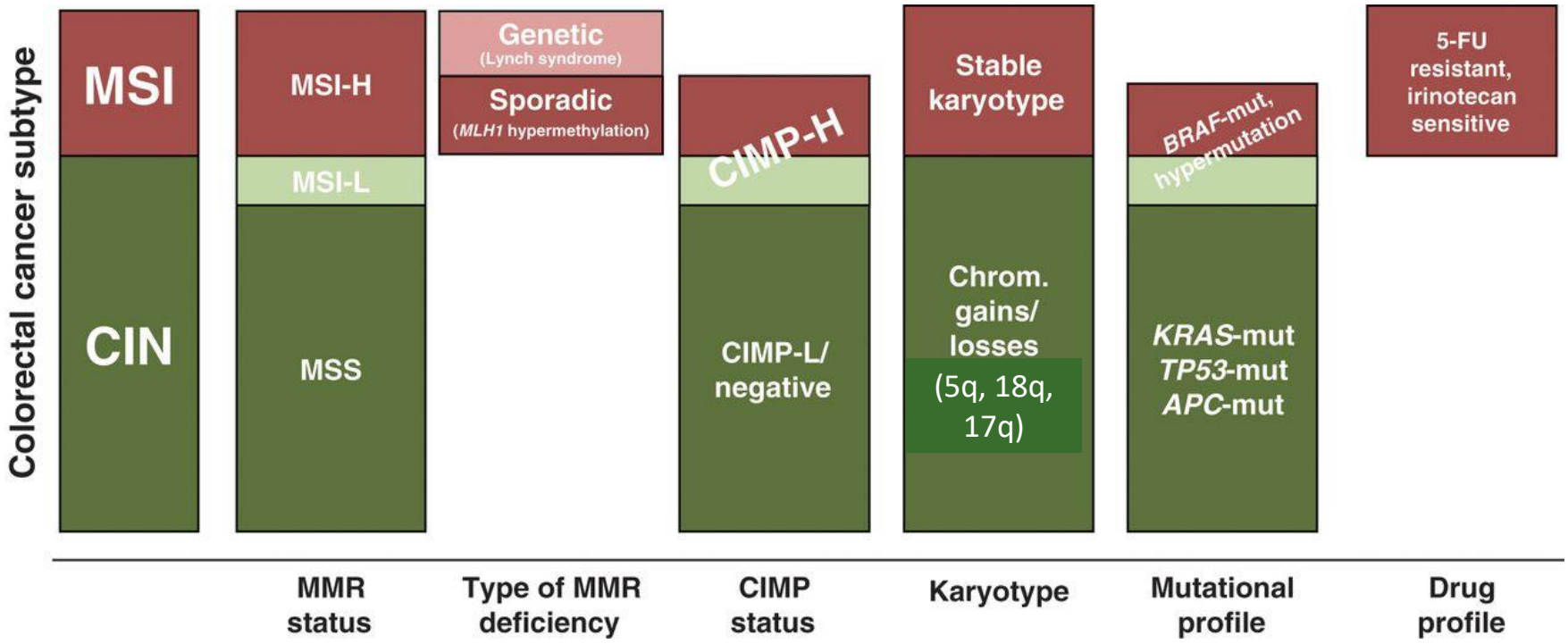
- Actionable molecular subtypes:
  - **HER2 positive** should be treated with trastuzumab[2]

1. U.S. FDA. Approved Drugs. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm577093.htm (accessed 12 March 2018). 2. Genentech Inc. Herceptin prescribing information. 2018. https://www.gene.com/download/pdf/herceptin_prescribing.pdf (accessed 12 March 2018)

FDA, Food and Drug Administration; HER2, human epidermal growth receptor 2; MSI, microsatellite instability; TCGA, The Cancer Genome Atlas.

COLORECTAL CANCER: SUBTYPES BY GENETICS

GI connect
POWERED BY COR2ED



Vilar et al. Cancer Discov. 2013; 3(5): 502–11.

5-FU, flourouracil; APC-mut, Adenomatous polyposis coli mutant; BRAF-mut, B-raf proto-oncogene mutant; CIMP, CpG island methylator phenotype; CIMP-H, CIMP high; CIMP-L, CIMP low; CIN, chromosomal instability; KRAS-mut, KRAS proto-oncogene, GTPase mutant; MLH1, MutL homolog 1; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSI-L, microsatellite instability low; MSS, microsatellite stable; TP53-mut, tumor protein p53 mutant.

COLORECTAL CANCER: RELEVANCE OF SUBTYPES BY GENETICS?

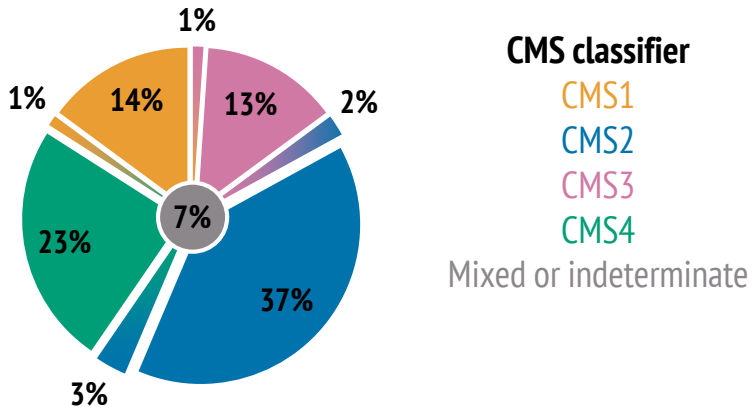
GI connect
POWERED BY COR2ED

- **RAS testing:**
  - EGFR antibodies ONLY in RASwt patients
- **BRAF testing:**
  - worst prognostic subgroup
  - BRAF inhibtor plus EGFR antibody?
- **MSI-H:**
  - immunecheckpoint-inhibitors
- **HER2/RASwt:**
  - HERCULES study: trastuzumab/lapatinib

BRAF, B-raf proto-oncogene; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability high; RASwt, Ras wild type.

CMS: SUBTYPES BY GENE-EXPRESSION

CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

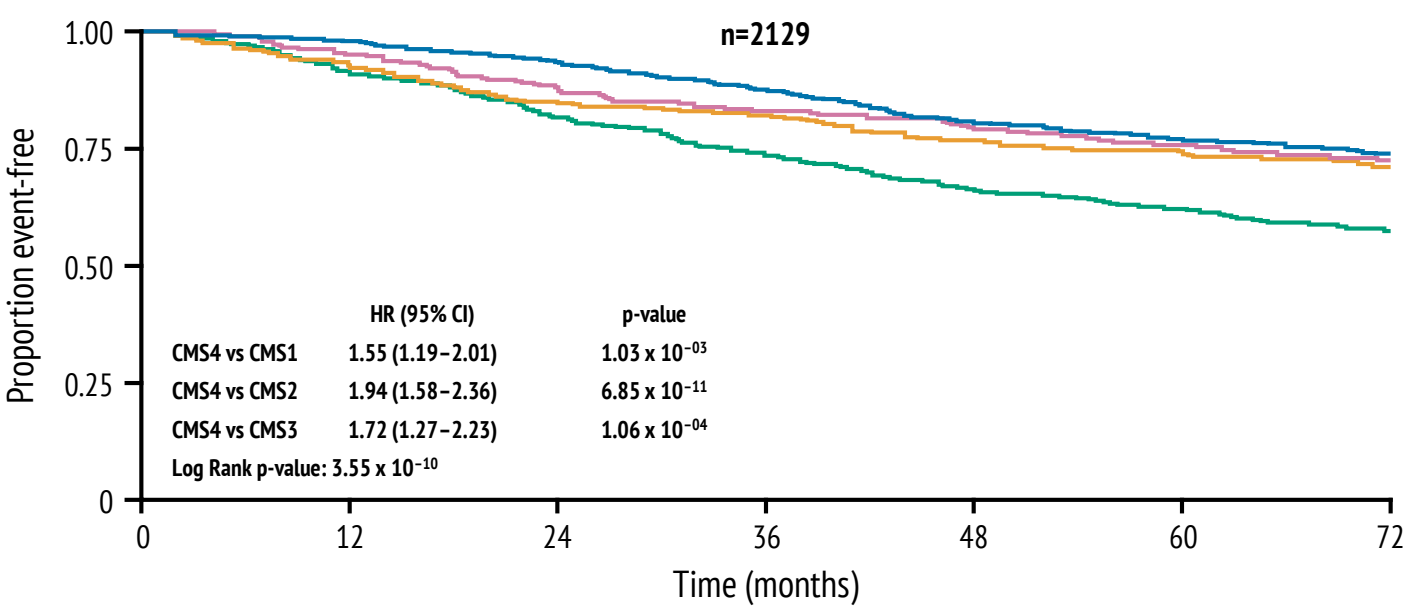


Molecular targeted therapy in gastrointestinal cancer – Sebastian Stintzing

Guinney J, et al. Nat Med 2015; 21: 1350–6

BRAF, B-raf proto-oncogene serine/threonine kinase; CIMP, CpG island methylator phenotype; CMS, consensus molecular subtype; KRAS, KRAS proto-oncogene, GTPase; MSI, microsatellite instability; MYC, MYC proto-oncogene; SCNA, somatic copy number alterations; TGF-β, transforming growth factor beta; WNT, Wnt proto-oncogene.

CMS: SUBTYPES BY GENE-EXPRESSION PROGNOSTIC IMPACT!



CMS1
MSI Immune

CMS2
Canonical

CMS3
Metabolic

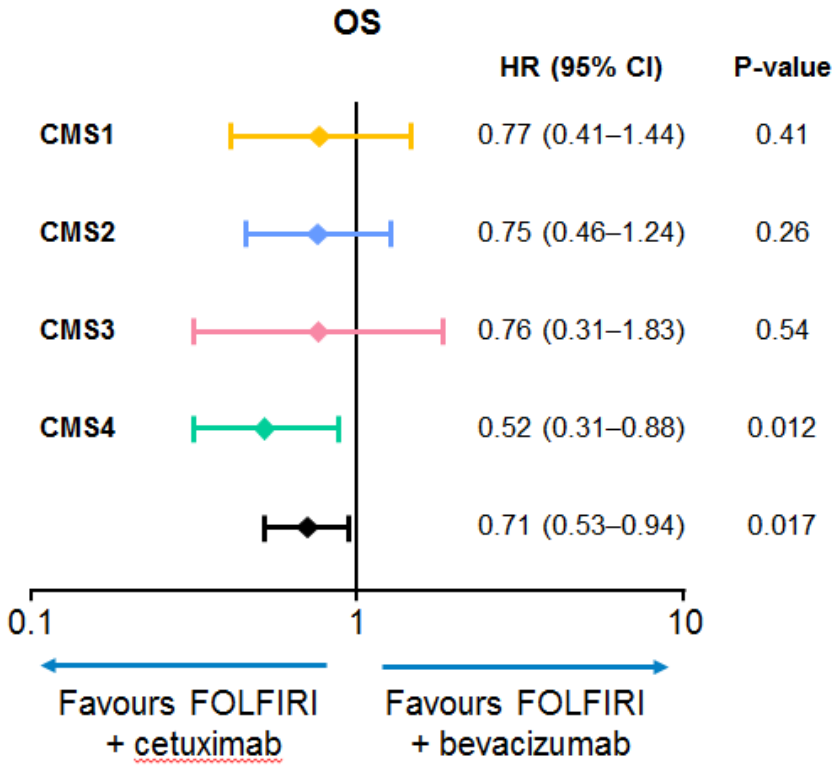
CMS4
Mesenchymal

Guinney J, et al. Nat Med. 2015; 21: 1350–6
CMS, consensus mollecular subtype; HR, hazard ratio.

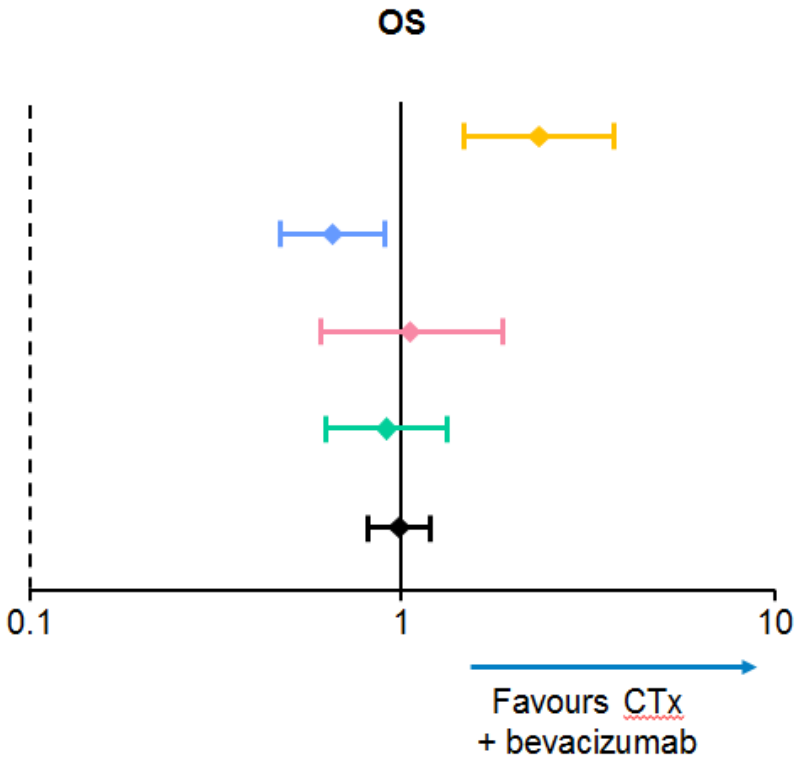
CMS: SUBTYPES BY GENE-EXPRESSION PREDICTIVE IMPACT?

GI connect
POWERED BY COR2ED

FIRE-3 (WT *RAS*)[1]



CALGB/SWOG 80405 (WT *KRAS*)[2]



1. Stintzing S, et al. J Clin Oncol. 2017; 35(Suppl): Abstract #3510 (oral presentation). 2. Lenz H-J, et al. J Clin Oncol. 2017; 35(Suppl): Abstract #3511 (oral presentation)
CALGB, Cancer and Leukemia Group B; CMS, consensus molecular subtype; Ctx, cetuximab; FIRE-3, FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer; KRAS, KRAS proto-oncogene, GTPase; OS, overall survival; SWOG, Southwestern Oncology Group; WT, wild type.

GI connect
POWERED BY COR2ED

GI CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com