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Supported by an Independent Educational Grant from BAYER

MEETING SUMMARY

ASCO GI, THURSDAY JANUARY 15TH 2015

BY DR. MED. SEBASTIAN STINTZING, MUNICH, GERMANY

Cancers of the Upper GI Tract

C-MET AS A TARGET IN GASTRIC CANCER

Two study results presented:

Abstract 1:

Clinical activity of AMG 337, a highly selective oral MET kinase inhibitor, in adult patients (pts) with MET-amplified gastroesophageal junction (GEJ), gastric (G), or esophageal (E) cancer.

Presenting Author: Eunice Kwak

Abstract 2:

Randomized phase II study of FOLFOX +/- MET inhibitor, onartuzumab (O), in advanced gastroesophageal adenocarcinoma (GEC).

Presenting Author: Manish A Shah

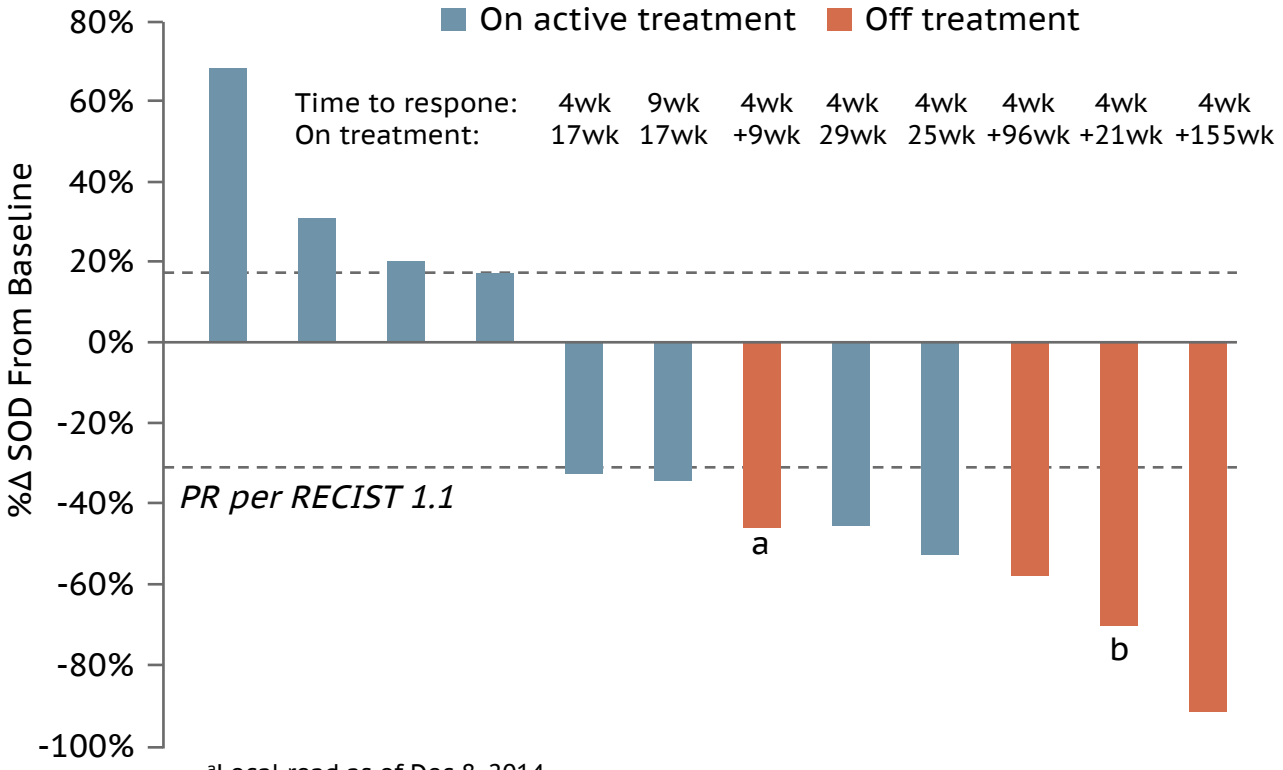
ABSTRACT 1

- Clinical activity of AMG 337, a highly selective oral MET kinase inhibitor, in adult patients (pts) with MET-amplified gastroesophageal junction (GEJ), gastric (G), or esophageal (E) cancer.

  Presenting Author: **Eunice Kwak**

- Data of a phase 1 trial with 90 Patients enrolled
- Patients with GC or cancer of the GEJ showed impressive results when cMet was amplified by FISH anaylsis
- A dose-expansion phase will enroll up to 50 patients with MET-amplified tumors at the MTD. Clinical trial information: NCT01253707

RECIST RESPONSES IN PATIENTS WITH MET-AMPLIFIED GEJ/GASTRIC/ESOPHAGEAL CANCER



- 13 patients with MET-amplified GEJ/gastric/ esophageal cancer treated to date;
  ORR = 8/13 (62%)

[a]Local read as of Dec 8, 2014.
[b]Local read as of Sept 10, 2014.
Central read as of Sept 18, 2014 for all other patients
One patient not shown with non-target lesions had clinical progression.

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ABSTRACT 2

- Randomized phase II study of FOLFOX +/- MET inhibitor, onartuzumab (O), in advanced gastroesophageal adenocarcinoma (GEC).

  Presenting Author: **Manish A Shah**

- Primary endpoint PFS
- N= 123

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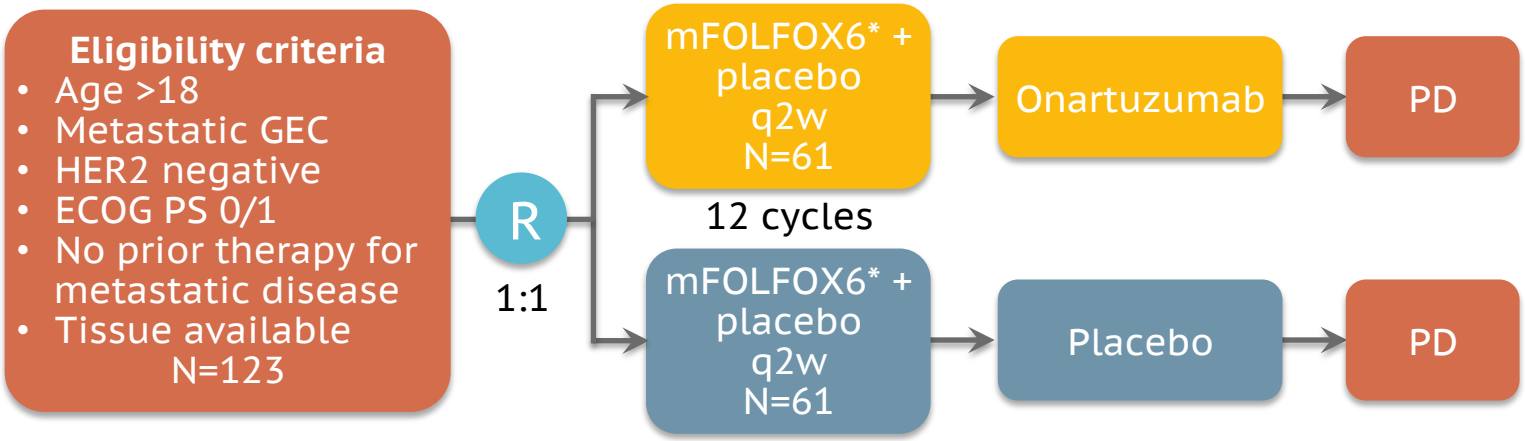
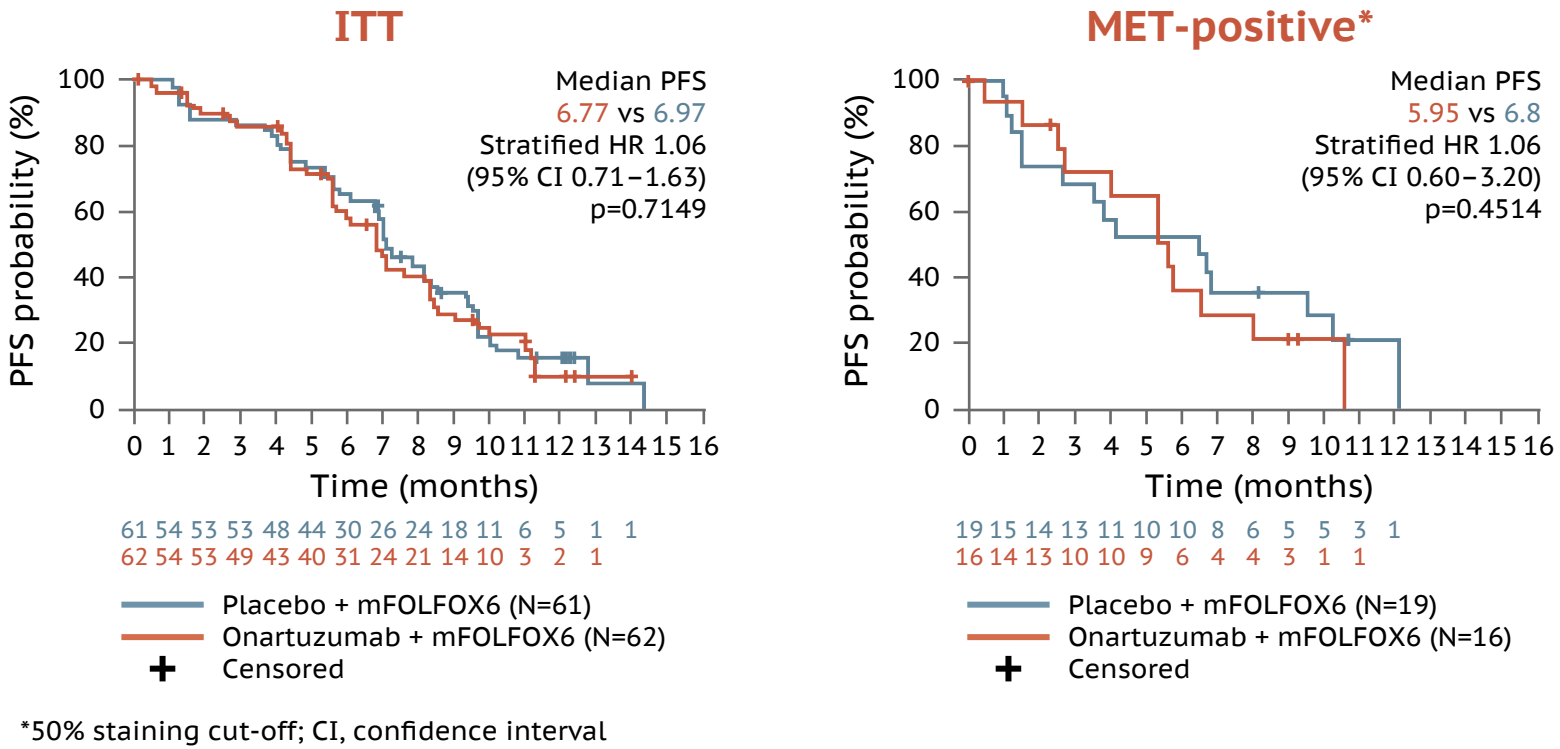
METHODS



- Stratified by Lauren histologic subtype and prior gastrectomy
- Primary objectives: **PFS in the ITT** population and the MET-positive subgroup (≥50% high staining by IHC)
- Secondary objectives: **OS** (ITT and MET-positive population), ORR, safety
- With 120 patients enrolled and 84 PFS events observed, target HRs were 0.70 in the ITT population and 0.60 in the MET-positive subgroup
- Conducted over 30 sites across Australia, Korea, Singapore, Taiwan, Thailand and USA

PRIMARY ENDPOINT: PFS



*50% staining cut-off; CI, confidence interval

- The stratified HR for PFS in the MET-negative population was 0.99 (95% CI 0.59–1.68)

CONCLUSIONS

- The addition of onartuzumab to mFOLFOX6 in metastatic GEC did not improve PFS in either an unselected population or in patients with MET-positive tumors

- The safety profile of onartuzumab was similar to previous studies: edema, venous thromboembolism, and Aes leading to treatment discontinuation were more frequent in the onartuzumab arm than the placebo arm

SUMMARY

- Obviously it matters, how you target c-Met: mAb or kinase inhibitor
- Companion diagnostic is important to define the patient population most likely to respond to your treatment

INTEGRATE:

A randomized phase II double-blind placebo-controlled study of regorafenib in refractory advanced oesophagogastric cancer (AOGC)— A study by the Australasian Gastrointestinal Trials Group (AGITG), first results

INTEGRATE

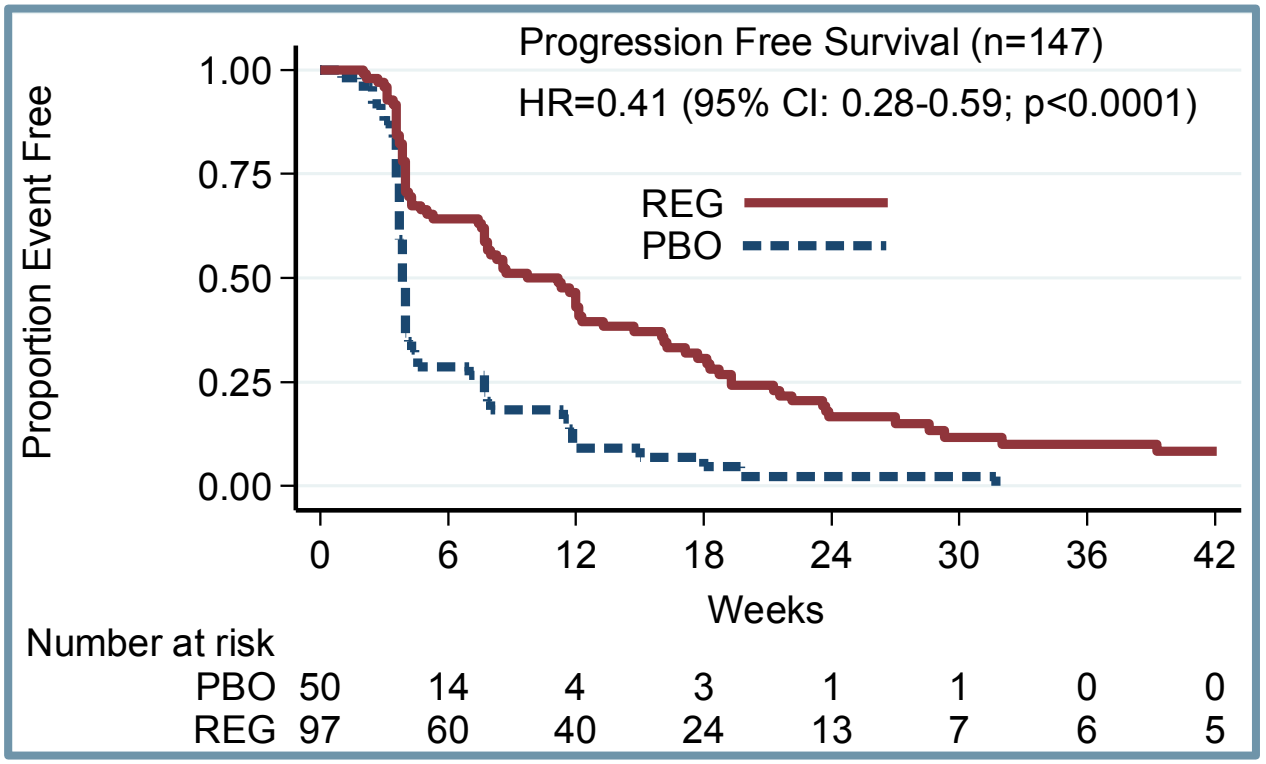
Background:

Advanced Oesophago-Gastric Carcinoma (AOGC) has limited options following failure of first or second line chemotherapy (CT). Regorafenib (REG) is an oral multi-kinase inhibitor of kinases involved in angiogenesis, tumor microenvironment, and oncogenesis. This study examined whether REG has sufficient activity and safety for further evaluation.

Methods:

International (Australia & New Zealand (ANZ), Korea, Canada (NCIC CTG)) randomised phase II trial with 2:1 randomisation and stratification by: (1) Lines of prior CT for advanced disease (1 vs. 2) and (2) Region. Eligible patients received best supportive care plus 160mg REG or matching PBO orally on days 1-21 each 28-day cycle until disease progression or prohibitive adverse events. Primary endpoint was progression free survival (PFS) in the REG arm, assuming median 8 weeks (wks) in PBO arm, aiming for 13.2 wks with REG to be of interest.

INTEGRATE, RESULTS



REG was well tolerated, with the spectrum of toxicity in keeping with previous reports.

INTEGRATE, CONCLUSIONS

- PFS was clearly significantly longer with REG than PBO, though PBO PFS was less than anticipated.
- The pre-specified exploratory comparisons provide compelling evidence that REG has sufficient activity with acceptable tolerability in refractory AOGC to warrant phase III evaluation.
- Mature OS results will be presented at the ASCO meeting.

ORAL SESSION 1

Abstract 7:

Comprehensive genomic profiling (CGP) of advanced stage esophageal squamous cell carcinomas (ESCC) and esophageal adenocarcinomas (EAC) reveals similarities and differences

Presenting Author: Kai Wang

Abstract 8:

Identification of the gastric microbiome from endoscopic biopsy samples using whole genome sequencing

Presenting Author: Chao Zhang

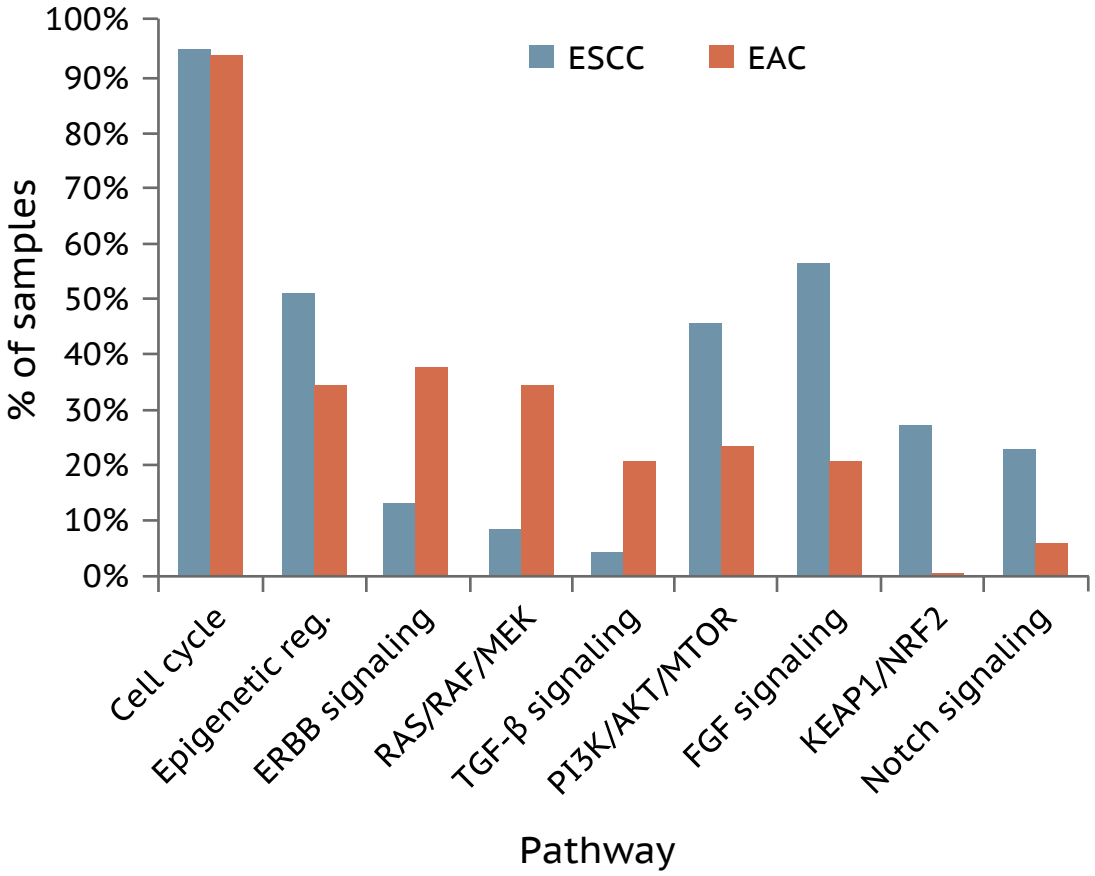
ABSTRACT 7

Methods (I)

- DNA was extracted from ~40u of FFPE sections from 71 ESCC and 231 EAC
- All samples are at advanced stages (III/IV)
- Comprehensive genomic profiling was performed on hybridization captured, adaptor ligation based libraries to a median coverage depth of ~650x for all coding exons of 236 cancer related genes plus 19 genes frequently rearranged in cancer
- The results were evaluated for all classes of genomic alterations (GA) including point mutations, short INDELs, copy number alterations and fusions/rearrangements
- Clinically relevant genomic alterations (CRGA) were defined as GA linked to drugs on the market or under evaluation in mechanism driven clinical trials

SIMILARITIES AND DIFFERENCES BETWEEN ESCC AND EAC

	ESCC	EAC	P Value
ERBB2	3%	23%	<0.0001
KRAS	6%	23%	0.0008
SMAD4	1%	14%	0.002
PTEN	11%	4%	0.03
PIK3CA	24%	10%	0.004
CCND1	42%	13%	<0.0001
NFE2L2	24%	1%	<0.0001
NOTCH1	17%	3%	0.0002
SOX2	18%	1%	0.0001
EGFR	8%	15%	0.2



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CONCLUSIONS

- Comprehensive genomic profiling indentifies potentially clinically relevant genomic alterations in advanced stage ESCC and EAC and that may drive the potential use of clinical outcome altering targeted therapies in both major types of esophageal cancer
- ESCC and EAC share high frequencies of total alterations and clinically relevant genomic alterations
- PI3K/mTOR (*PIK3CA* and *PTEN*) and Notch pathway genes are significantly enriched in ESCC, and RAS/MEK pathway genes (*ERBB2* and *KRAS*) are significantly enriched in EAC
- HPV16 was detected in 2 (3%) and HPV18 in 2 (3%) of ESCC. Neither HPV or *H. pylori* was detected in EAC
- Driver mutant gene prevalence in ESCC shows significant difference from several published results, which may indicate distinct genetic mechanisms due to stage of disease at the time of sequencing, environment, ethnicity and treatment history factors (poster A7)

ABSTRACT 8

The microbiome of the stomach

Dr. Chao Zhang performed WGS from small biopsy samples of the stomach and identified:

- A relationship between H. pylori infection and gastric microbiome
- Differences in the microbiome between normal mucosa and cancer sample

CONCLUSION

- Microbiome can be detected by low-pass WGS from small biopsy sample
- Stringent filtering of human DNA reads and coverage evaluation are necessary for detecting microbiome in samples with low bacteria levels
- Prior treatment of *H. pylori* infection may not fully clear the infection

SUMMARY

- Tumor site and etiology of cancer are important determinants of the molecular profile and identification of relevant druggable targets
- Environmental factors such as infection, bile reflux, and smoking are important cancer risk modifiers that are site specific
- The complexity of interaction between the host environment, microbiome, and the genetics are likely to be risk modifier factors. Future cancer prevention and therapeutic strategies may take these into account
- **Combined strategies that take into account the genetic and biological features of the tumors is the future of personalized medicine in cancer therapy**

Adapted from Wael El-Rifai