GI SLIDE DECK 2015

Selected Abstracts on **Non-Colorectal Cancer** from:

esdo european society of digestive oncology

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Letter from ESDO

DEAR COLLEAGUES

It is my pleasure to present this ESDO slide set which has been designed to highlight and summarise key findings in digestive cancers from the major congresses in 2015. This slide set specifically focuses on Non-Colorectal Cancer from the American Society of Clinical Oncology Annual Meeting.

The area of clinical research in oncology is a challenging and ever changing environment. Within this environment, we all value access to scientific data and research which helps to educate and inspire further advancements in our roles as scientists, clinicians and educators. I hope you find this review of the latest developments in digestive cancers of benefit to you in your practice. If you would like to share your thoughts with us we would welcome your comments. Please send any correspondence to info@esdo.eu.

And finally, we are also very grateful to Lilly Oncology for their financial, administerial and logistical support in the realisation of this activity.

Yours sincerely,

Eric Van Cutsem
Wolff Schmiegel
Phillippe Rougier
Thomas Seufferlein

(ESDO Governing Board)

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european society of digestive oncology

ESDO Medical Oncology Slide Deck
Editors 2015

COLORECTAL CANCERS



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PANCREATIC CANCER AND HEPATOBILIARY TUMOURS


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GASTRO-OESOPHAGEAL AND NEUROENDOCRINE TUMOURS


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BIOMARKERS


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esdo

Glossary

5FU	5-fluorouracil
ADC	adenocarcinoma
AE	adverse event
AFP	alpha-fetoprotein
ALT	alanine transaminase
AOGC	advanced oesophagogastric cancer
AST	aspartate aminotransferase
bid	twice daily
BSC	best supportive care
CI	confidence interval
CF	cisplatin/5-fluorouracil
CLIP	Cancer of the Liver Italian Program
CR	complete response
CT	chemotherapy
ctDNA	circulating tumour DNA
DCR	disease control rate
DFS	disease-free survival
DGAC	diffuse gastric adenocarcinoma
DOR	duration of response
ECF	epirubicin/cisplatin/5-fluorouracil
ECOG	Eastern Cooperative Oncology Group
ECX	epirubicin/cisplatin/capecitabine
EGFR	endothelial growth factor receptor
FGFR	fibroblast growth factor receptor
FISH	fluorescence in situ hybridisation
FLOT	docetaxel/5-fluorouracil/leucovorin/oxaliplatin
FOLFIRINOX	leucovorin, fluorouracil, irinotecan, oxaliplatin
FOLFOX	oxaliplatin, fluorouracil, and leucovorin
GEC	gastroesophageal adenocarcinoma
GEJ	gastroesophageal junction
GI	gastrointestinal
HA	hyaluronan
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HR	hazard ratio
ICC	intrahepatic cholangiocarcinoma
IFN	interferon
IHC	immunohistochemistry
ITT	intent-to-treat
IV	intravenous
KPS	Karnofsky Performance Status
mAb	monoclonal antibody
MR	minor response
MSI	microsatellite instability
NLR	neutrophil-lymphocyte ratio
OC	oesophageal cancer
ORR	overall response rate
(m)OS	(median) overall survival
PAG	PEGPH20 + nab-paclitaxel/gemcitabine
PCR	polymerase chain reaction
PCR-NGS	PCR-next generation sequencing
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death-ligand 1
PDAC	pancreatic ductal adenocarcinoma
PET	positron emission tomography
(p)NET	(pancreatic) neuroendocrine tumour
(m)PFS	(median) progression free survival
PR	partial response
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
RFS	relapse-free survival
RR	response rate
RT	radiotherapy
SAE	serious adverse event
SR	subtotal response
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
TSD	tumour stroma density
TTF	time to treatment failure
TTP	time to progression
ULN	upper limit of normal
QoL	quality of life
SCC	squamous cell carcinoma
SD	stable disease
VEGF	vascular endothelial growth factor

Contents

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HEPATOCELLULAR CARCINOMA

4011: Hepatitis B- and C-associated hepatocellular carcinoma in a large U.S. cancer center: Do clinicopathologic features or patient outcomes differ by the potentially causative viruses? – Uemura MI, et al

Study objective

- To investigate the clinical characteristics and survival outcomes in patients with hepatitis B virus (HBV) and hepatitis C virus (HCV) hepatocellular carcinoma (HCC) regardless of therapy received

Study design

- Retrospective, large-scale, single-centre study performed at the MD Anderson Cancer Centre (Houston, TX) involving 815 patients with HCC (HCV n=472, HBV n=343) between 1992–2011
- Diagnosis confirmed: pathological (n=713) or radiological (n=102)
- Chi-square test was used to assess the differences in distribution of categorical variables between the HBV and HCV groups
- Median survival was calculated using Kaplan Meier product-limit method and survival rates were compared using the log rank test

Uemura et al. J Clin Oncol 2015; 33 (suppl): abstr 4011

4011: Hepatitis B- and C-associated hepatocellular carcinoma in a large U.S. cancer center: Do clinicopathologic features or patient outcomes differ by the potentially causative viruses? – Uemura MI, et al

Key results

Clinical and pathological characteristics in HCV and HBV

	Age (years), mean±SD	Poorly differentiated tumour, %	Portal thrombosis, %	Tumour size (>5 cm), %	Tumour volume (>50%), %	Cirrhosis, %	CLIP (4–6), %	Smoking, %	Alcohol, %	Type 2 diabetes, %	Systemic therapy, %	Local therapy, %	AFP (IU/ml), mean±SD
HCV	61.3±10	18.8	30.2	35.2	26.6	86.0	15.8	73.0	70.1	23.5	27.5	27.5	17,894±4,662
HBV	57.4±14	26.5	35.7	49.4	42.9	59.5	25.0	56.1	49.3	18.3	39.6	17.6	55,708±1,0950
p-value	<0.001	0.001	0.05	0.02	<0.001	<0.001	0.008	<0.001	<0.001	0.05	<0.001	<0.001	<0.001

- Median OS was 10.9 and 9.3 months for HCV and HBV, respectively (p=0.9)

Conclusion

- **Incidence of advanced clinicopathological features was significantly higher in patients with HCC and HBV than HCV, which may impact a patient's eligibility for treatment, but not prognosis**

Uemura et al. J Clin Oncol 2015; 33 (suppl): abstr 4011

Similarities and differences in hepatocellular carcinoma: Etiology and other factors – Abou-Alfa GK

Discussion of abstract 4011

- To understand the aetiology of HCC and associate it with the demographics and genetics of the disease
  - Aetiology of HCC differs at the molecular level between HBV, HCV, alcohol and obesity
  - Demographics may partly predict underlying HCC aetiology
- There a number of different scoring systems available for HCC (Child-Pugh, Okuda, CLIP, CUPI, TNM6, JIS, GRETCH and BCLC), some of which are aetiology specific
- Putting this data in context, previous studies have shown that different treatment-related outcomes can be recognised based on HCC aetiology:
  - The phase 3 SHARP trial showed a significantly longer OS with sorafenib vs. placebo (10.7 vs. 7.9 months, HR 0.69 [95%CI 0.55, 0.87]; p<0.001), which was driven by HCV-HCC
  - Nivolumab has shown steady kinetics with regards to change in target lesion in HCV-HCC vs. HBV-HCC
  - Expression of MET can be used as a prognostic factor for OS

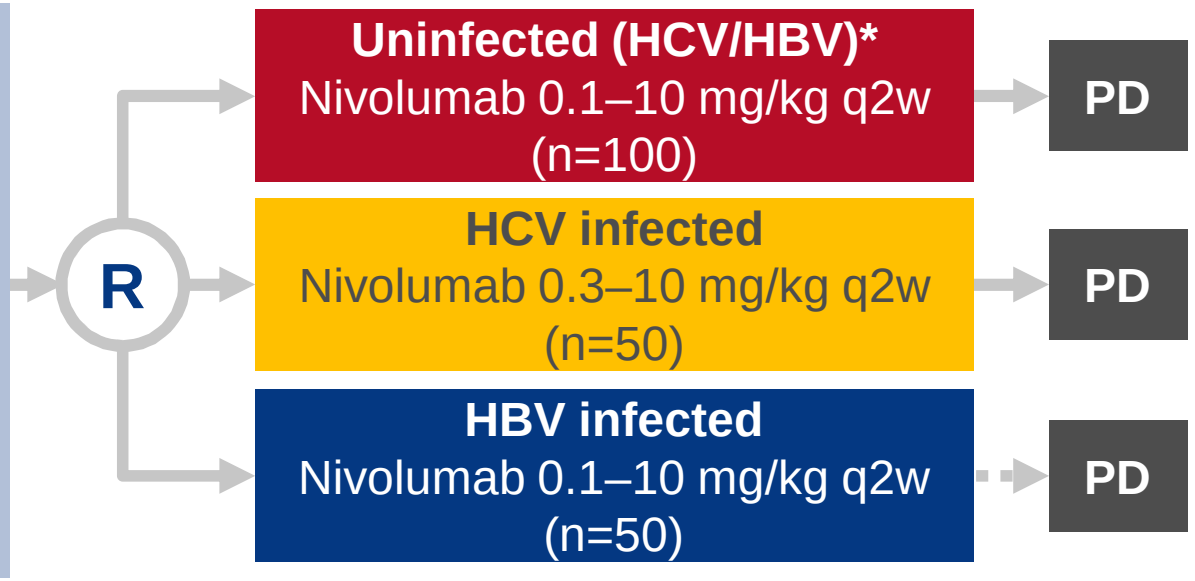
LBA101: Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040 – El-Khoueiry AB, et al

Study objective

- To assess the efficacy and safety of the anti-PD-1 mAb nivolumab in patients with advanced HCC with either progression after systemic therapy or sorafenib intolerance

Key patient inclusion criteria
- Advanced HCC
- Child Pugh A or B
- Progression after ≥1 first-line therapy or intolerant to sorafenib
- AST/ALN ≤5x ULN
- Bilirubin ≤3 mg/dL

(n=200)



PRIMARY ENDPOINTS

- Safety, dose-limiting toxicities, maximum tolerated dose

SECONDARY ENDPOINT

- ORR

- Study comprised a phase 1 dose escalation phase and a phase 2 expansion phase
  - 3 kg/mg dose was selected for all groups (except HBV infected) for expansion phase

*Sorafenib progressors or sorafenib-naïve patients (n=50 each)

El-Khoueiry et al. J Clin Oncol 2015; 33 (suppl): abstr LBA101

LBA101: Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040 – El-Khoueiry AB, et al

Key results

- Prior use of sorafenib therapy was: 63% in uninfected; 50% in HCV and 100% in HBV

TEAEs in ≥5% patients, %	Any grade	Grade 3	Grade 4
AST increased	19	11	0
Lipase increased	17	6	2
Rash	17	0	0
ALT increased	15	9	0
Amylase increased	15	0	0
Pruritus	13	0	0
Hypoalbuminemia	9	0	0
Anaemia	6	2	0
Fatigue	6	2	0
Asthenia	6	0	0
Diarrhoea	6	0	0
Hyponatremia	6	0	0

- No grade 5 TEAEs were reported

El-Khoueiry et al. J Clin Oncol 2015; 33 (suppl): abstr LBA101

LBA101: Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040 – El-Khoueiry AB, et al

Key results (cont.)

	Uninfected (n=21)	HCV (n=11)	HBV (n=42)
ORR, %	14	36	10
CR	10	0	0
PR	5	36	10
SD	48	45*	50
PD	38	18	40
Ongoing response, %	100	75	0

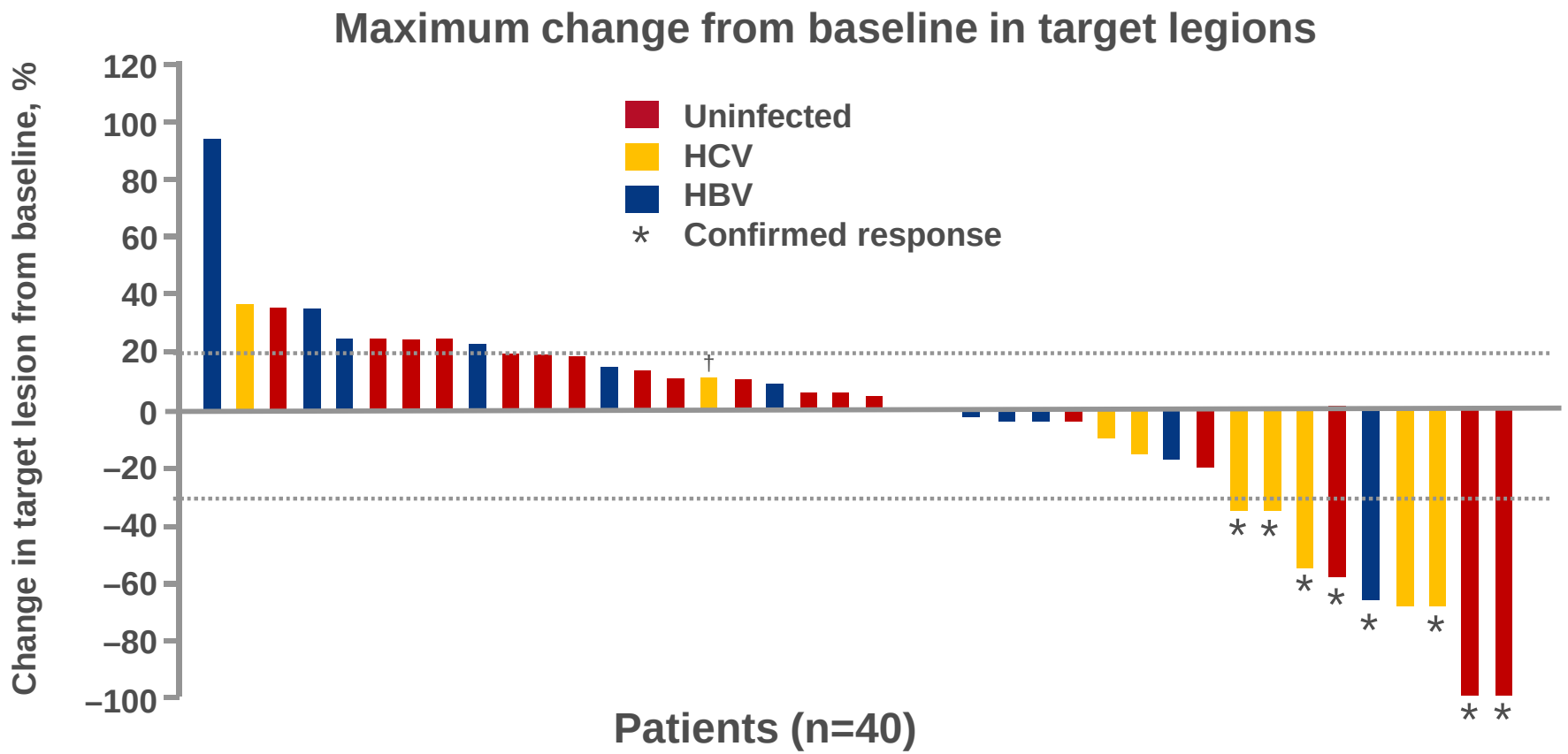
*Patient with resolved HCV infection

OS rate, % (95%CI)	Total (n=47)
9-month	70 (52, 82)
12-month	62 (42, 76)

El-Khoueiry et al. J Clin Oncol 2015; 33 (suppl): abstr LBA101

LBA101: Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040 – El-Khoueiry AB, et al

Key results (cont.)

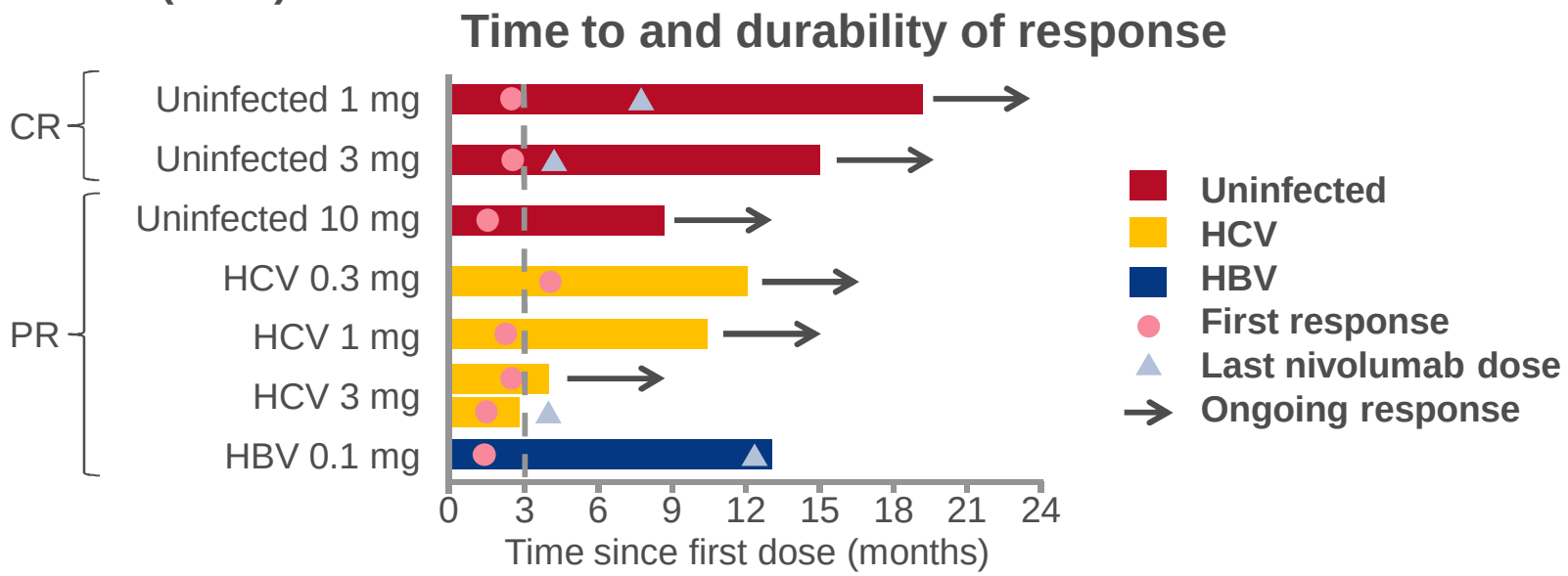


†Patient with resolved HCV infection

El-Khoueiry et al. J Clin Oncol 2015; 33 (suppl): abstr LBA101

LBA101: Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209-040 – El-Khoueiry AB, et al

Key results (cont.)



Conclusions

- Nivolumab had a manageable safety profile in patients with advanced HCC, including those with HCV or HBV infection
- Durable responses were observed in hepatitis infected and uninfected patients
- 12-month OS rates with nivolumab were encouraging
- These preliminary data support the ongoing dose expansion phase and continued exploration of nivolumab in patients with HCC

El-Khoueiry et al. J Clin Oncol 2015; 33 (suppl): abstr LBA101

4018: A randomized, double-blind, placebo-controlled phase III study of S-1 in patients with sorafenib-refractory advanced hepatocellular carcinoma (S-CUBE) – Kudo M, et al

Objective

- To verify the superiority of S-1 treatment vs. placebo in Japanese patients with sorafenib-refractory advanced HCC

Key patient inclusion criteria

- Sorafenib-refractory* advanced HCC
- Ineligible for surgical or local-regional therapy
- ≥1 target lesion
- Child-Pugh score 5–7
- ECOG PS 0–1

(n=334)

R 2:1

S-1
40–60 mg bid D1–28
(n=222)

PD

Stratification

- Medical institution
- Extrahepatic metastasis and/or vascular invasion

Placebo
(n=111)

PD

PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- PFS, TTF, ORR, safety

*Discontinued sorafenib treatment due to PD or AE

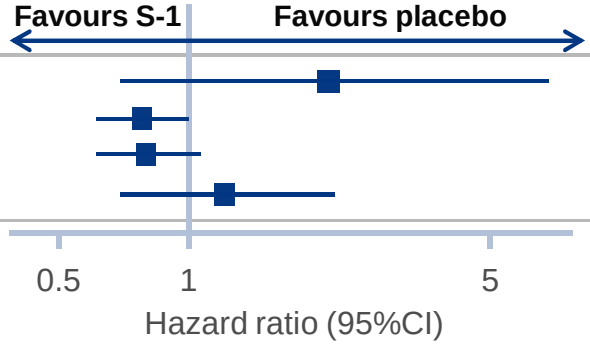
Kudo et al. J Clin Oncol 2015; 33 (suppl): abstr 4018

4018: A randomized, double-blind, placebo-controlled phase III study of S-1 in patients with sorafenib-refractory advanced hepatocellular carcinoma (S-CUBE) – Kudo M, et al

Key results

	S-1	Placebo	HR (95%CI)	p-value
mOS, days	337.5	340.0	0.86 (0.67, 1.10)	0.2201
mPFS, days	80.0	42.0	0.60 (0.46, 0.77)	<0.0001
ORR, %	5.4	0.9		0.068

		S-1 events/N	Placebo events/N	Hazard ratio (95%CI)	p-value
TNM stage	I/II	13/38	4/9	2.08 (0.67, 6.42)	0.0969
	III/IV	170/204	96/102	0.79 (0.61, 1.02)	
Child-Pugh class	A	143/180	81/90	0.79 (0.60, 1.04)	0.1119
	B	40/42	19/21	1.19 (0.68, 2.09)	



- Any grade AEs (occurring in >25%) with S-1 were: decreased appetite, fatigue, increased blood bilirubin, diarrhoea, nausea, peripheral oedema, ascites

Conclusions

- **S-1 did not improve OS vs. placebo in patients with sorafenib-refractory advanced HCC**
- **S-1 improved OS in a subgroup of patients with stage III/IV + Child-Pugh A HCC**
- **Most AEs of S-1 were manageable and mild to moderate in severity**

Kudo et al. J Clin Oncol 2015; 33 (suppl): abstr 4018

4020: Multi-institutional phase II study of high dose, hypofractionated proton beam therapy (HF-PBT) for unresectable primary liver cancers: Long term outcomes in patients (pts) with intrahepatic cholangiocarcinoma (ICC) – Hong TS, et al

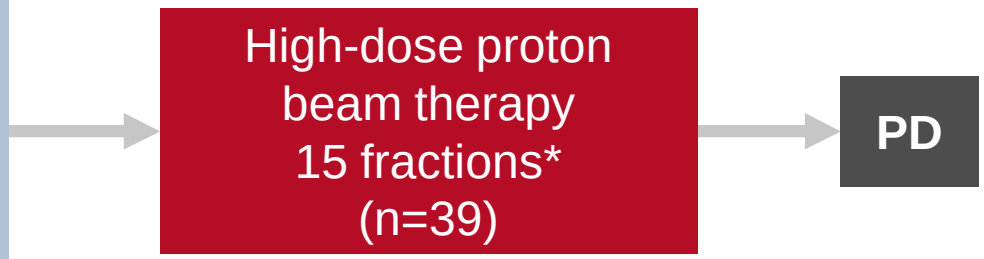
Objective

- To assess long-term survival outcomes with high-dose proton beam therapy in patients with unresectable ICC

Key patient inclusion criteria

- Unresectable ICC
- No cirrhosis or Child-Pugh A/B
- ECOG PS 0–2
- No extrahepatic disease
- No prior RT
- Tumour size ≤12 cm

(n=43)



*Peripheral 67.5 Gy, central (≤2 cm porta hepatis) 58 Gy, dose de-escalated based on Veff of uninvolved liver

Hong et al. J Clin Oncol 2015; 33 (suppl): abstr 4020

4020: Multi-institutional phase II study of high dose, hypofractionated proton beam therapy (HF-PBT) for unresectable primary liver cancers: Long term outcomes in patients (pts) with intrahepatic cholangiocarcinoma (ICC) – Hong TS, et al

Key results

- Median follow-up duration among 19 survivors: 13.2 months (range 0.6–50.4 months)

	1-year, %	2-year, %
Local control	97	90
OS	69	44
PFS	40	28

PFS status	%
Local only	12.8
Local + haematogenous	2.6
Haematogenous	48.7
Death, no progression	10.3
Alive, no progression	25.6

Conclusion

- **High-dose protein beam therapy for patients with unresectable ICC resulted in high rates of local control and OS**
- **These data forms the basis for the ongoing NRG GI-001 study**

Hong et al. J Clin Oncol 2015; 33 (suppl): abstr 4020

Hepatobiliary cancers: Looking through the prism – Kelley RK

Discussion of abstract 4018

- *Why were PFS and RR improved but not OS (primary endpoint)?*
  - It is difficult to blind drugs with characteristic symptomatic toxicity (e.g. diarrhoea) and a lack of true blinding can influence local assessments
  - In the placebo group, the extremely short mPFS (1.5 months) was in contrast to the very long mOS (12.1 months), which may have been owing to local assessment of clinical progression; potentially due to an awareness of placebo allocation
- *Why did second-line placebo OS outcome exceed expectation?*
  - The drop out of poor prognosis subsets during first-line therapy, leaving better prognosis patients to enter second-line trials
  - In addition, the study population was notable for enrichment with clinical features associated with favourable prognosis (intermediate stage ~30%, <20% vascular invasion)
- The long placebo OS in this study is a reminder that the study population matters
  - Future second-line studies should be conducted in carefully defined, similar populations

Conclusion

- **S-1 did not improve OS, but provides an important benchmark for contemporary second-line HCC outcomes in a Japanese cohort**

Hepatobiliary cancers: Looking through the prism – Kelley RK

Discussion of abstract 4020

- Local control rates exceeded OS and PFS rates at 1- and 2-years, due to censoring of deceased patients with local control regardless of extrahepatic disease
- High local control rates must be interpreted in the context of the overall tumour status
  - High rates of extrahepatic spread was common in this population
  - Local complication rate (i.e. biliary obstruction, hepatic failure) is a meaningful endpoint
- Where does proton beam therapy fit among the other local therapy options?
  - Comparative studies for each modality are not feasible
  - Instead, pooled analyses with carefully defined endpoints are necessary
  - Prospective trials require pragmatic “lumping” (i.e. NRG GI-001: allows SBRT, IMRT, or PBT) for accrual

Conclusions

- **Proton beam therapy has promising local control and safety rates – among many other local therapy options**
- **The upcoming NRG GI-001 trial will determine if adding radiation to systemic therapy improves survival in unresectable intrahepatic cholangiocarcinoma**

OESOPHAGEAL AND GASTRIC CANCER

4002: Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: Results from the UK Medical Research Council randomised OEO5 trial (ISRCTN 01852072) – Alderson D, et al

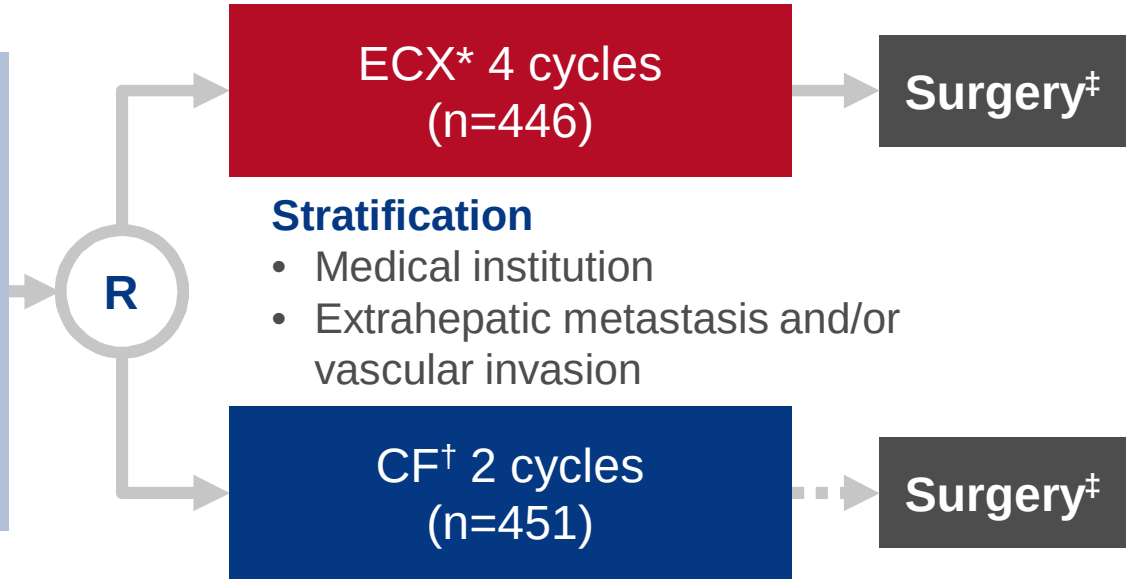
Study objective

- To determine whether epirubicin/cisplatin/capecitabine (ECX) improve outcomes in patients with oesophageal cancer compared with cisplatin/5FU (CF)

Key patient inclusion criteria

- Histologically confirmed oesophageal or oesophogastric junction adenocarcinoma
- Resectable

(n=897)



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- DFS, PFS, pathological R0 resection rate, Mandard grade and QoL

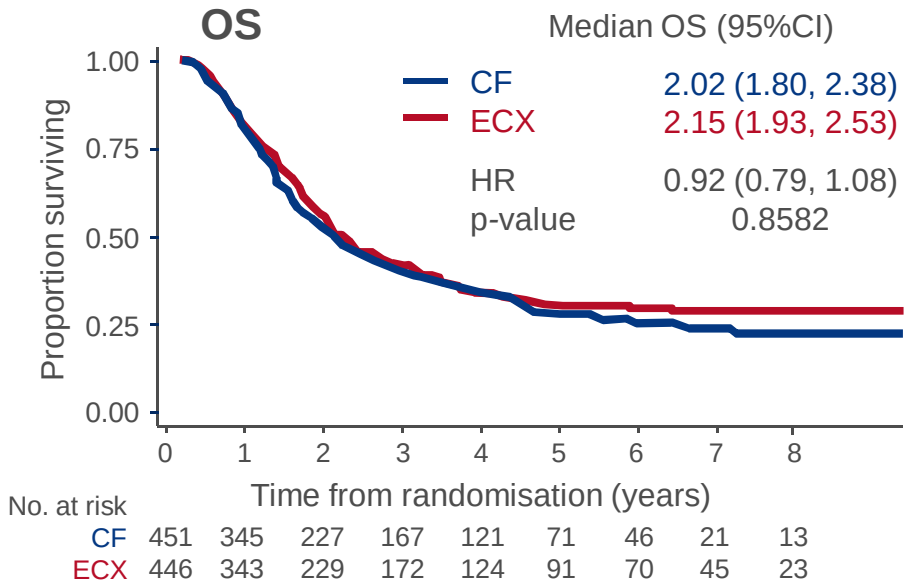
*Epirubicin 50 mg/m^2 D1, cisplatin 60 mg/m^2 D1, capecitabine 1,250 mg/m^2/day; †cisplatin 80 mg/m^2 D1, 5FU 1 g/m^2 D1–4; ‡oesophagectomy with 2-field lymphadenectomy for lower oesophageal and junctional (types I and II) adenocarcinoma

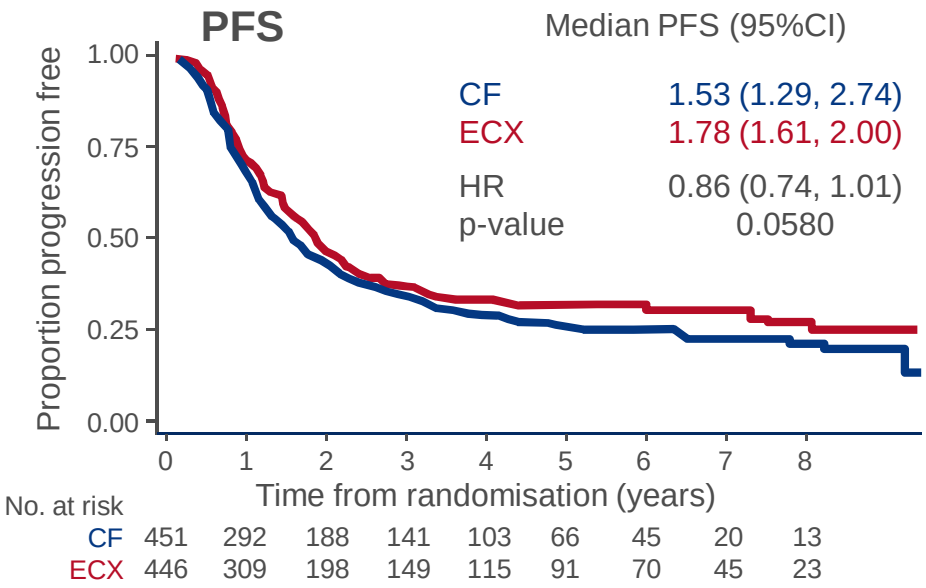
Alderson et al. J Clin Oncol 2015; 33 (suppl): abstr 4002

4002: Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: Results from the UK Medical Research Council randomised OEO5 trial (ISRCTN 01852072) – Alderson D, et al

Key results

- 89% of ECX patients received >3 cycles, while 96% of CF group received 2 cycles
- Among patients undergoing resection, R0 rates were 67% ECX vs. 60% CF (p=0.059), with tumour regression (assessed by Mandard grade ≤3) achieved in 32% ECX vs. 15% CF (p<0.001)
  - 11 vs. 3% patients achieved complete response
- 3-year survival rates were similar: 42% ECX vs. 39% CF





Alderson et al. J Clin Oncol 2015; 33 (suppl): abstr 4002

4002: Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: Results from the UK Medical Research Council randomised OEO5 trial (ISRCTN 01852072) – Alderson D, et al

Key results (cont.)

- Postoperative complications were similar (ECX 62% vs. CF 57%) as were deaths at 30 (ECX 2%, CF 2%) and 90 days post-surgery (ECX 5% vs. CF 4%)
- Overall grade 3/4 toxicity was higher with ECX than CF (47 vs. 30%; $p<0.001$)
  - There were significantly higher rates of grade 3/4 diarrhoea ($p<0.001$), neutropenia ($p<0.001$), infection/febrile neutropenia ($p=0.007$) and PPE ($p<0.001$) with ECX vs. CF and significantly higher rates of grade 3/4 stomatitis ($p=0.002$) with CF vs. ECX

Conclusions

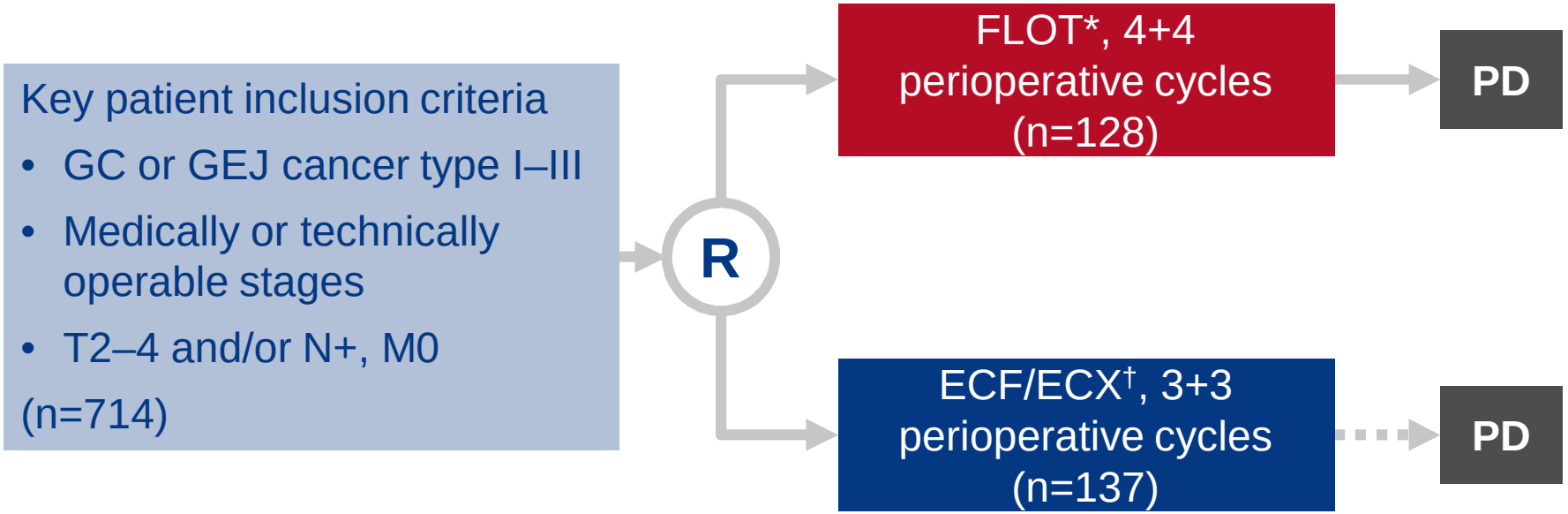
- **Treatment with ECX resulted in a trend towards prolonged PFS and DFS and a higher tumour regression at resection compared with CF, but this did not translate into a benefit in OS**
- **ECX had higher toxicity compared with CF**
- **The two regimens (ECX and CF) may be used as neoadjuvant treatment**

Alderson et al. J Clin Oncol 2015; 33 (suppl): abstr 4002

4016: 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 – Pauligk C, et al

Objective

- To assess pathological responses with neoadjuvant FLOT vs. ECF or ECX in patients with locally advanced, resectable gastric or GEJ adenocarcinoma



- Pathological samples from 157 patients of the phase 2 part of the study were analysed
  - Central pathology was performed according to Becker classification

*Docetaxel 50 mg/m² D1, 5FU 2,600 mg/m² D1, leucovorin 200 mg/m² D1, oxaliplatin 85 mg/m², D1, q2w ; †Epirubicin 50 mg/m² D1, cisplatin 60 mg/m² D1, 5FU 200 mg/m² (or capecitabine 1,250 mg/m² po) D1–21 q3w)

Pauligk et al. J Clin Oncol 2015; 33 (suppl): abstr 4016

4016: 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 – Pauligk C, et al

Key results

Pathological remission, % (ITT population)	FLOT (n=128)	ECF/ECX (n=137)	p-value
CR	15.6	5.8	0.015
Subtotal response (SR; <10% residual)*	21.1	16.8	-
CR+SR	36.7	22.6	0.015
PR (10–50% residual)	18.0	20.4	-
Minor response (MR; >50% residual)	35.2	32.1	-
No response	3.1	5.8	-
Not resectable	7.0	19.0	-

Conclusion

- FLOT was associated with significantly higher rates of complete pathological remission vs. ECF/ECX in patients with locally advanced, resectable gastric cancer or GEJ adenocarcinoma
- The phase 3 part of the study will determine whether pathological remission is associated with improved survival

Pauligk et al. J Clin Oncol 2015; 33 (suppl): abstr 4016

Resectable gastric and esophageal cancer: Increasing the likelihood of cure – Ilson DH

Discussion of abstract 4016

- Is pathological response to preoperative CT a surrogate for survival?
  - Previous studies indicate that high pathological responses do not translate to an OS benefit
- How do we interpret the pathological response data for FLOT vs. ECF/ECX?
  - Phase 2 data are very encouraging, but OS and response data are pending the full trial analysis
  - However, pathological response to preoperative CT is not currently a validated endpoint
- Future directions
  - Further large adjuvant trials studying CT permutations in OC may not be warranted
  - Instead, the focus should be on developing novel targeted agents
    - e.g. VEGF-targeted agents (MAGIC B trial); HER2-directed agents (phase 2/3 studies are ongoing); immunotherapy
  - Validated biomarkers are also needed to guide therapy selection (e.g. PET scan to direct treatment)

4000: Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study – Cunningham D, et al

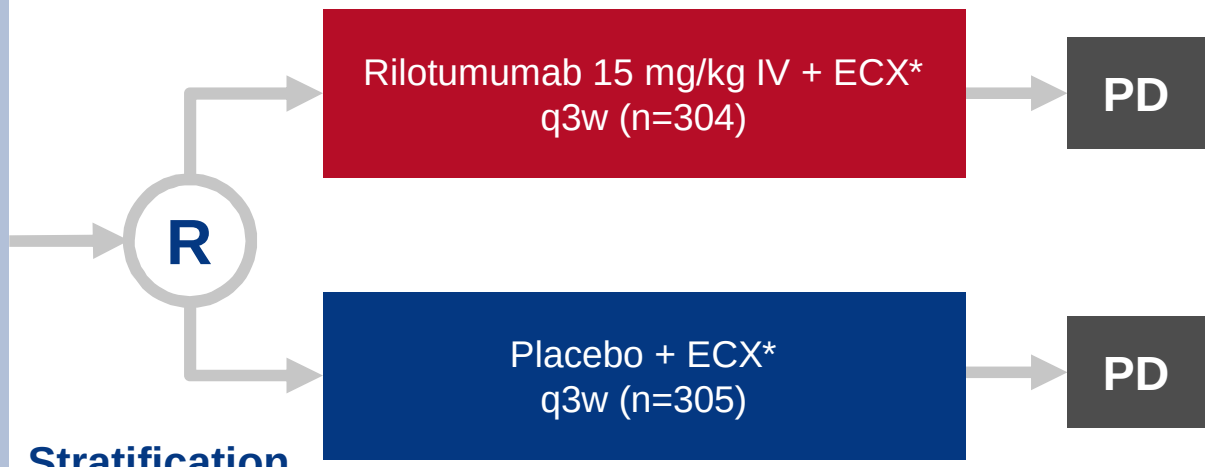
Study objective

- To evaluate the efficacy and safety of rilotumumab + epirubicin/cisplatin/capecitabine (ECX) as first-line treatment in patients with *MET*+ advanced gastric or gastroesophageal junction cancer (G/GEJ)

Key patient inclusion criteria

- Age ≥18 years
- No prior therapy
- Pathologically confirmed unresectable advanced or metastatic G/GEJ adenocarcinoma
- ECOG PS 0–1
- Tumour *MET*+ by IHC
- HER2-negative

(n=609)



Stratification

- Disease extent (locally advanced vs. metastatic)
- ECOG PS (0 vs. 1)

PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- PFS, ORR, DCR, safety and pharmacokinetics

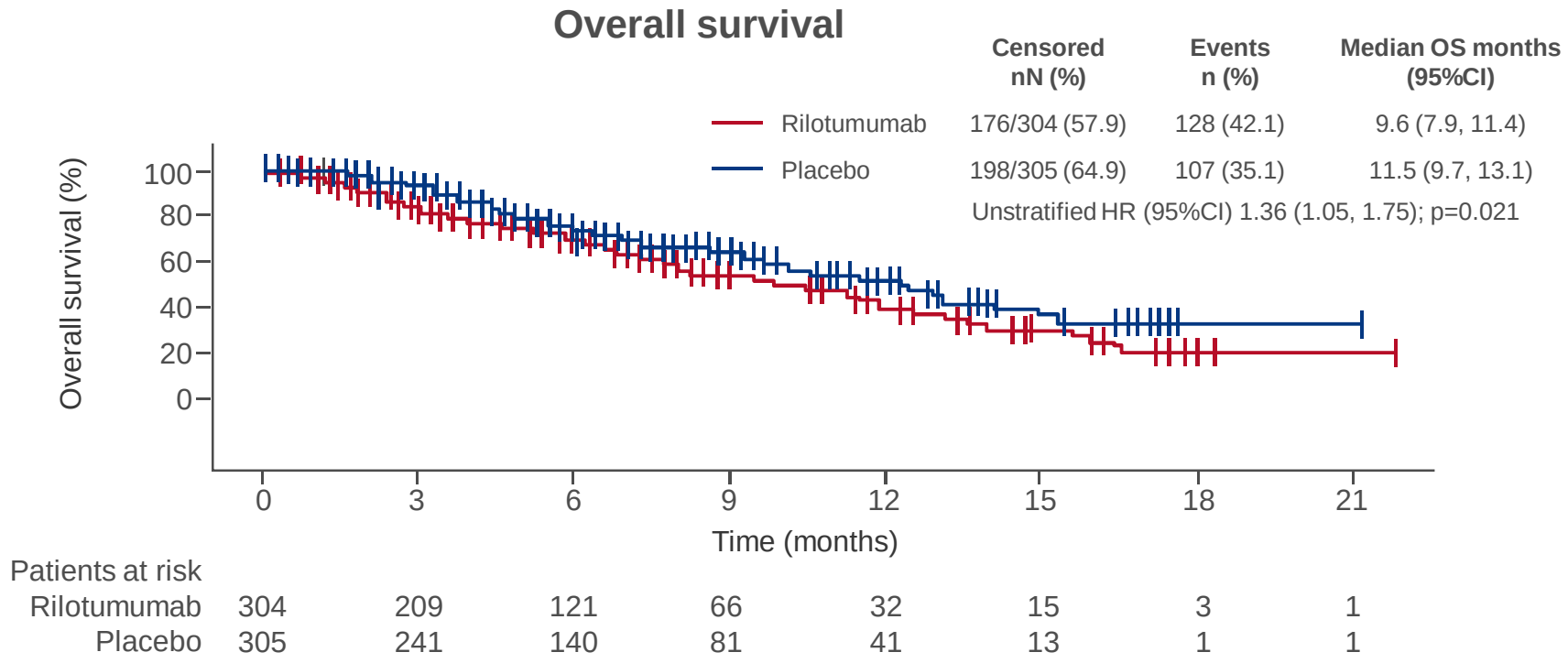
*Epirubicin 50 mg/m^2 IV D1; cisplatin 60 mg/m^2 IV D1; capecitabine 625 mg/m^2 bid orally, D1−21

Cunningham et al. J Clin Oncol 2015; 33 (suppl): abstr 4000

4000: Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study – Cunningham D, et al

Key results

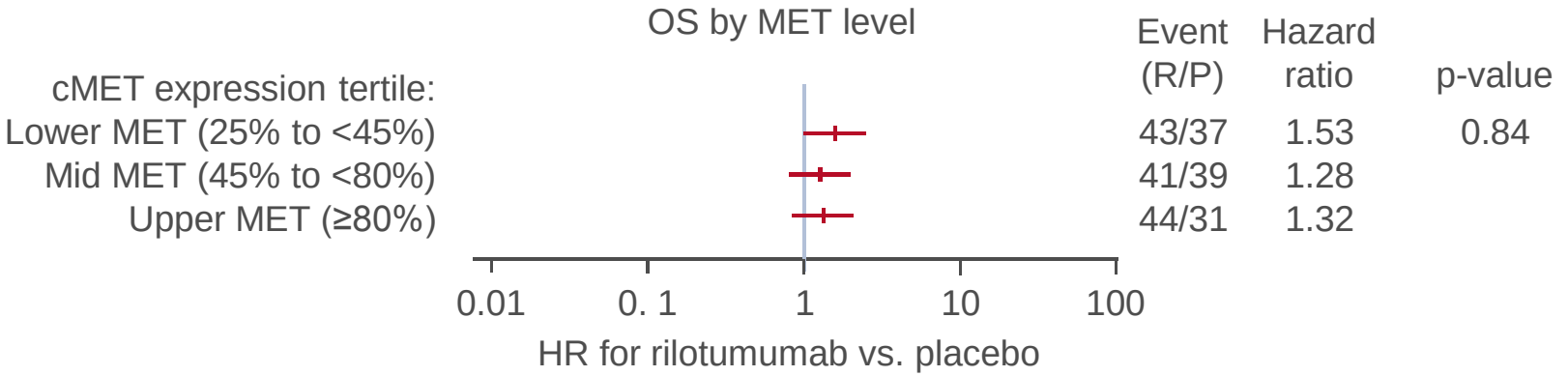
- The study was stopped early based on an imbalance in deaths (rilotumumab vs. placebo: 128 vs. 107 deaths, data cut-off: 27 Nov 2014) primarily due to disease progression



Cunningham et al. J Clin Oncol 2015; 33 (suppl): abstr 4000

4000: Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study – Cunningham D, et al

Key results (cont.)



- No subgroups within the selected *MET*+ population saw a benefit in OS with rilotumumab, including those with higher percentages of cells with ≥1+ *MET* expression
- AEs that were significantly higher in the rilotumumab arm were: peripheral oedema (28.5 vs. 12.0%), hypoalbuminemia (11.1% vs. 2.7%), deep vein thrombosis (9.1 vs. 3.3%) and hypocalcaemia (9.4 vs. 2.3%)

Conclusion

- **RILOMET-1 did not meet its primary endpoint; survival was significantly worse with rilotumumab in previously untreated patients with MET+ G/GEJ cancer regardless of the MET+ expression level**

Cunningham et al. J Clin Oncol 2015; 33 (suppl): abstr 4000

4001: Relationship between PD-L1 expression and clinical outcomes in patients with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) in KEYNOTE-012 – Bang YJ, et al

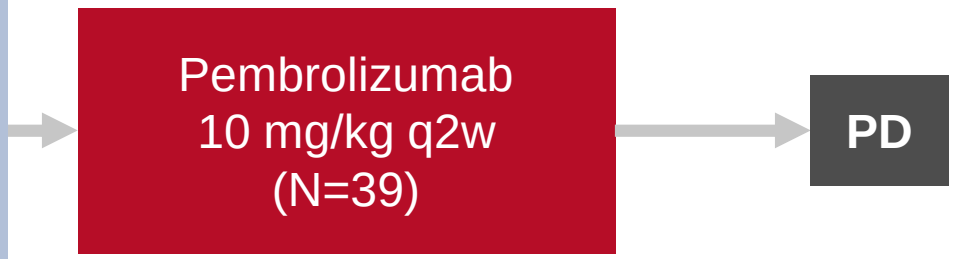
Study objective

- To assess the safety and efficacy of the anti-PD-1 monoclonal antibody pembrolizumab in patients with PD-L1-positive advanced gastric cancer in the KEYNOTE-012 trial

Key patient inclusion criteria

- Recurrent or metastatic adenocarcinoma of the stomach or GEJ
- ECOG PS 0–1; PD-L1*-positive
- No systemic steroid therapy
- No autoimmune disease or active brain metastases

(n=65)



- Archived tumour samples were screened for PD-L1 expression using an IHC-based assay

Presented at ASCO GI: Muro et al. J Clin Oncol 2015; 33 (suppl 3; abstr 3)
Bang et al. J Clin Oncol 2015; 33 (suppl): abstr 4001

4001: Relationship between PD-L1 expression and clinical outcomes in patients with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) in KEYNOTE-012 – Bang YJ, et al

Key results

- AEs occurred in 26/29 (66.7%) patients
  - Most frequent (occurring in >7%) were: fatigue (17.9%), decreased appetite (12.8%), hypothyroidism (12.8%), nausea (7.7%) and pruritus (7.7%)
- Grade 3–5 treatment-related AEs occurred 4/39 (10.3%) patients
  - Grade 3: decreased appetite, fatigue, periphery sensory neuropathy (each n=1)
  - Grade 4: pneumonitis (n=1); Grade 5: hypoxia (n=1), resulting in death

Best overall response (RECIST v1.1)	Central review (N=36)	Investigator review (N=39)
ORR, % (95% CI)	22.2 (10.1, 39.2)	33.3 (19.1, 50.2)
Best overall response, n (%)		
CR	0	0
PR	8 (22.2)	13 (33.3)
SD	5 (13.9)	5 (12.8)
PD	19 (52.8)	21 (53.8)

Presented at ASCO GI: Muro et al. J Clin Oncol 2015; 33 (suppl 3; abstr 3)
Bang et al. J Clin Oncol 2015; 33 (suppl): abstr 4001

4001: Relationship between PD-L1 expression and clinical outcomes in patients with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) in KEYNOTE-012 – Bang YJ, et al

Key results (cont.)

- 6-month PFS rate: 24%; 6-month OS rate: 69%
- mPFS: 1.9 (95% CI 1.8, 3.5) months; mOS: not reached
- A trend towards improved OS, ORR and PFS was observed with higher levels of PD-L1 expression, although this did not reach statistical significance

Conclusions

- **Pembrolizumab had an acceptable safety and tolerability profile in patients with PD-L1-positive advanced gastric cancer**
- **Pembrolizumab demonstrated a durable antitumour response in 22% of patients assessed by RECIST v1.1**
- **There was a trend towards improved overall response with higher PD-L1 expression**

Presented at ASCO GI: Muro et al. J Clin Oncol 2015; 33 (suppl 3; abstr 3)
Bang et al. J Clin Oncol 2015; 33 (suppl): abstr 4001

4003: 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)—Final overall and subgroup results – Pavlakis N, et al

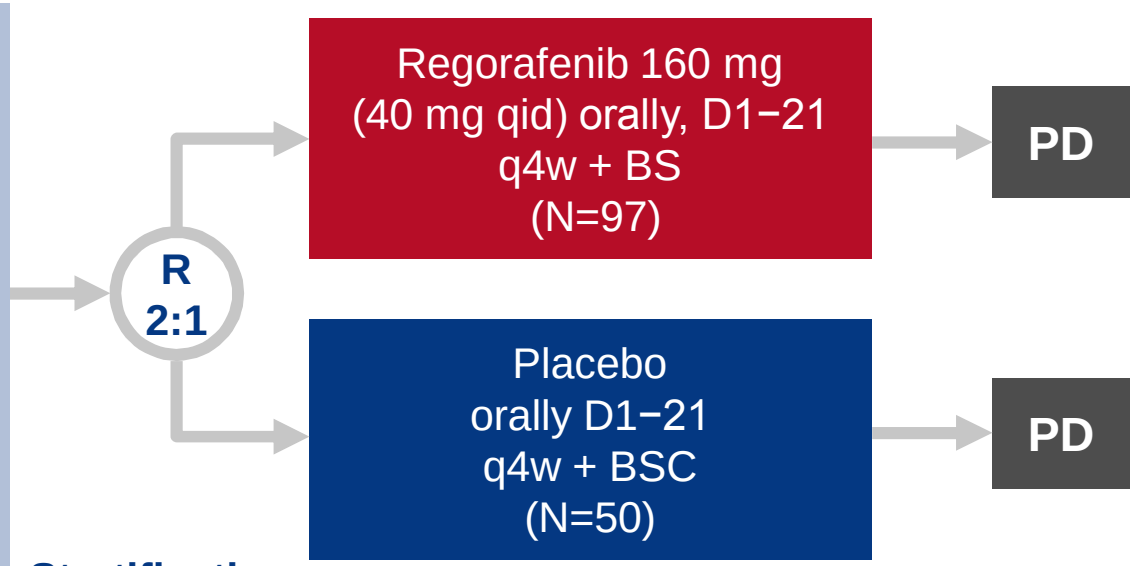
Study objective

- To evaluate the efficacy and safety of regorafenib in refractory advanced oesophagogastric cancer (AOGC) following failure of 1st or 2nd line chemotherapy

Key patient inclusion criteria

- Metastatic or locally recurrent AOGC occurring in any primary oesophagogastric site and is of adenocarcinoma or undifferentiated carcinoma histology
- Measurable according to RECIST v1.1
- Refractory to 1st or 2nd line chemotherapy
- ECOG PS 0–1

(n=152)



Stratification

- Line of therapy (1st vs. 2nd)
- Geographic region

PRIMARY ENDPOINT

- PFS

SECONDARY ENDPOINTS

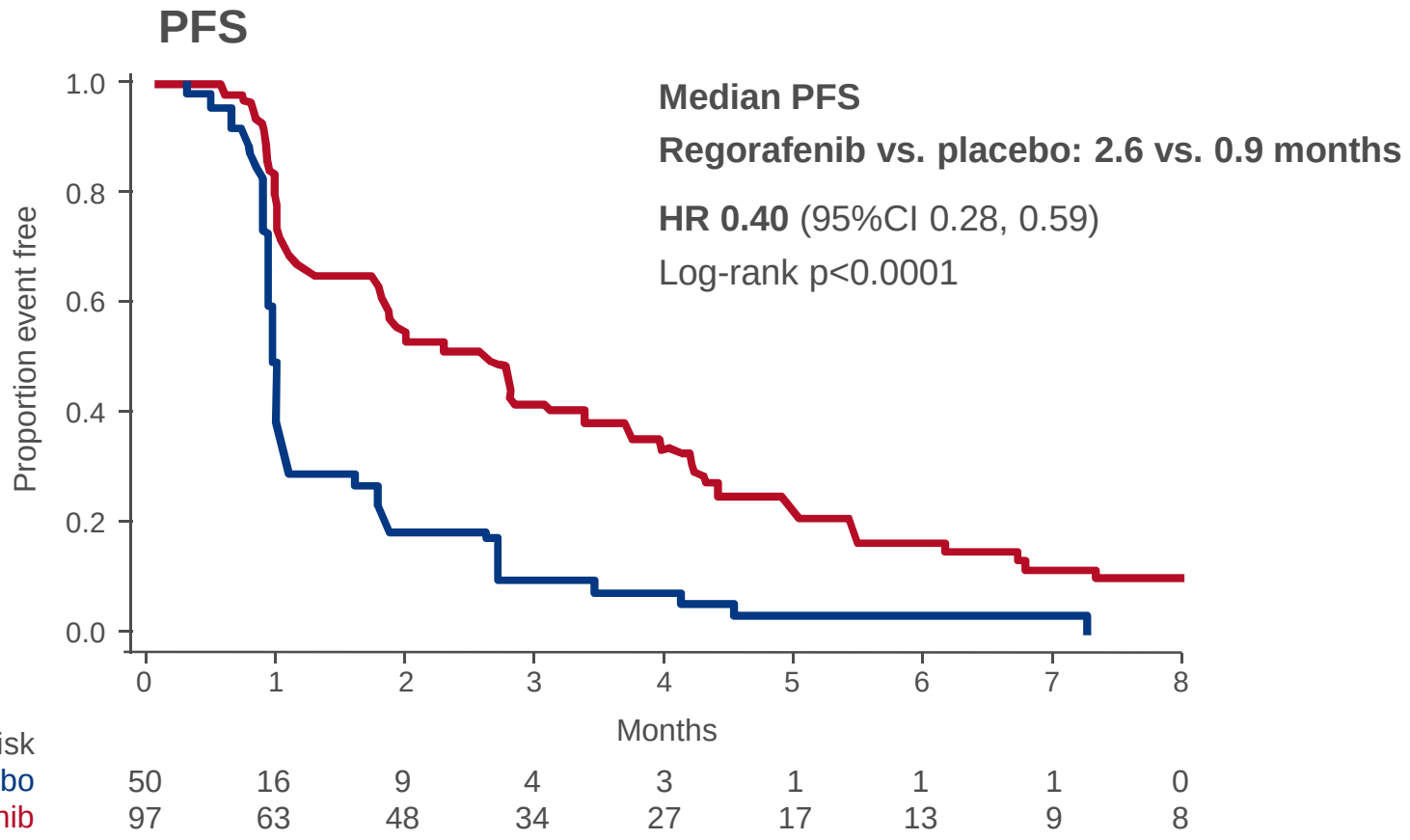
- Objective tumour response rate, clinical benefit at 2 months, OS, safety, QoL

Pavlakis et al. J Clin Oncol 2015; 33 (suppl): abstr 4003

4003: 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)—Final overall and subgroup results – Pavlakis N, et al

Key results

- Median OS for regorafenib vs. placebo was 5.8 vs. 4.5 months (HR 0.74 [95%CI 0.51, 1.08]; p=0.11)



Pavlakis et al. J Clin Oncol 2015; 33 (suppl): abstr 4003

4003: 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)—Final overall and subgroup results – Pavlakis N, et al

Key results (cont.)

Key subgroups	PFS HR (95%CI)	p-value	Interaction p-value
ANZ/Canada (n=93)	0.61 (0.39, 0.97)	0.0324	0.0009
Korea (n=54)	0.12 (0.06, 0.27)	<0.0001	
Lines of prior therapy			
1st (n=62)	0.49 (0.28, 0.86)	0.01	0.50
2nd (n=85)	0.32 (0.19, 0.55)	<0.0001	
Neutrophil-lymphocyte ratio (NLR)			
<3 (n=71)	0.41 (0.23, 0.70)	0.0007	0.72
≥3 (n=76)	0.37 (0.22, 0.64)	0.0001	
Plasma VEGF-A (pg/mL)			
Low (≤0.14), (n=82)	0.39 (0.24, 0.65)	0.0001	0.72
High (>0.14), (n=62)	0.42 (0.23, 0.78)	0.005	

- Grade 3–5 AEs occurring in ≥5% of the regorafenib arm included: anorexia, hypertension, abdominal pain, increased aspartate aminotransferase and increased alanine aminotransferase

Conclusion

- **In this phase 2 study, regorafenib was highly effective in all regions and subgroups prolonging PFS, with a trend towards a longer OS, but a confirmatory phase 3 trial is required**

Pavlakis et al. J Clin Oncol 2015; 33 (suppl): abstr 4003

Searching for positive signals in gastroesophageal cancer – Ku GY

Discussion of abstract 4000

- Inferior outcomes were seen in the RILOMET-1 study compared with results from the randomised phase 2 trial[1] that preceded RILOMET-1
  - Differences in baseline factors such as a higher proportion of patients with gastro-oesophageal junction (GEJ) tumours and fewer Asian patients in RILOMET-1 and the choice of antibodies used for IHC (more patients found to be MET-positive in RILOMET-1) could account for the differences observed in survival outcomes between the two studies
- RILOMET-1 and the phase 2 trial[1] provide no rational for additional evaluation of anti-MET pathway antibodies in biomarker-selected oesophageal gastric cancer populations

Discussion of abstract 4001

- The study reported encouraging survival rates in a group of patients with tumours over-expressing PD-L1 who were treated with the anti-PD-1 antibody pembrolizumab
- KEYNOTE-012 corroborated the significant activity observed with immune checkpoint inhibitors in oesophageal gastric cancer
  - PD-L1 IHC has been proposed as a biomarker but this remains to be validated
  - Alternatively gene signatures have been proposed to be predictive of response and survival

1. Shah et al. J Clin Oncol 2015; 33 (suppl): abstr 02

Searching for positive signals in gastroesophageal cancer – Ku GY

Discussion of abstract 4002

- The OEO5 study revealed no OS benefit for the intensification of preoperative therapy with the epirubicin, cisplatin and capecitabine (ECX) regimen vs. 5FU/cisplatin, although there was a trend towards improvement in PFS
  - No role for antracyclines as preoperative therapy for oesophageal/GEJ adenocarcinoma
  - No benefit for prolonged chemotherapy with fluoropyrimidine/platinum
  - No benefit of induction chemotherapy prior to preoperative chemoradiation
  - Preoperative fluoropyrimidine/platinum for 6 weeks for oesophageal/GEJ adenocarcinoma remains a standard of care
- Important to identify and validate a biomarker early in clinical development of a drug

Discussion of abstract 4003

- The INTEGRATE study showed that there was a significant difference in PFS for 2nd or 3rd line regorafenib, but not OS possibly because the study was under powered and patients could be switched to regorafenib
- A phase 3 trial with regorafenib is warranted and should include patients who have been treated with ramucirumab to provide real-world applicability of the results (regorafenib has shown activity in the CORRECT study in chemo-refractory patients who had received bevacizumab)
- Although these benefits must be weighted against toxicity and financial impact of end-of-life medications

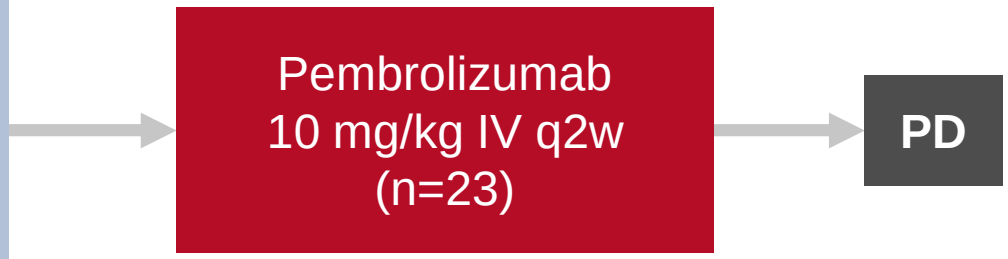
4010: Pembrolizumab (MK-3475) for patients (pts) with advanced esophageal carcinoma: Preliminary results from KEYNOTE-028 – Doi T, et al

Study objective

- To assess the efficacy and safety of pembrolizumab (anti-PD-1 mAb) in patients with PD-L1+ oesophageal carcinoma

Key patient inclusion criteria

- SCC or ADC of the oesophagus or GEJ
- PD-L1 positivity*
- Failure of standard therapy
- ECOG PS 0–1
- ≥1 measurable legion
- No autoimmune disease



PRIMARY ENDPOINTS

- ORR per RECIST v1.1
- Safety

SECONDARY ENDPOINTS

- PFS, OS, duration of response

*≥1% of cells in tumour nests or PD-L1+ stromal bands

Doi et al. J Clin Oncol 2015; 33 (suppl): abstr 4010

4010: Pembrolizumab (MK-3475) for patients (pts) with advanced esophageal carcinoma: Preliminary results from KEYNOTE-028 – Doi T, et al

Key results

Efficacy outcomes	Pembrolizumab (n=23)
ORR, % (95% CI)	30.4 (13.2, 52.9)
CR	0.0 (0.0, 14.8)
PR	30.4 (13.2, 52.9)
SD, % (95% CI)	13.0 (2.8, 33.6)
PD, % (95% CI)	56.5 (34.5, 76.8)
Median time to response, weeks (range)	16.0 (7.9, 36.0)
Median duration of response, weeks (range)	40.0 (0.1, 40.0)

Grade 3–4 AEs, n (%)	Pembrolizumab (n=23)
Any (all grade 3)	4 (17.4)
Lymphocytes decreased	2 (8.7)
Appetite decreased	1 (4.3)
Liver disorder	1 (4.3)
Pruritic rash	1 (4.3)

- ORR by histology: 29.4% for SCC and 40.0% for adenocarcinoma
- 52.2% patients showed reduced target lesion burden with pembrolizumab

Conclusions

- **Pembrolizumab provided promising anti-tumour activity and had a manageable toxicity profile in patients with heavily pre-treated, PD-L1+ advanced oesophageal carcinoma**
- **Further investigation of pembrolizumab treatment in oesophageal carcinoma is warranted**

Doi et al. J Clin Oncol 2015; 33 (suppl): abstr 4010

Potential practice effects of gastric and esophageal cancer subtyping – Fuchs CS

Discussion of abstract 4010

- The incidence of OC is increasing in the US whereas oesophageal SCC is declining
- A high rate of focal amplifications exist in upper vs. lower GI cancers
  - OC has a distinct pattern of amplifications vs. oesophageal SCC
- Elevated PD-L1 and PD-L2 expression is observed in EBV^{+} MSI-high gastric cancer
  - A number of agents targeting PD-1 and PD-L1 are currently in development
- In the current study, pembrolizumab appeared to be efficacious and well tolerated
  - These data are encouraging and appear to be similar to data in gastric cancer
  - Larger studies are now needed with adequate power to examine both SCC and ADC
- Comprehensive evaluation of predictive biomarkers of PD-1 efficacy in OC is critical
  - PD-L1 expression is a predictive biomarker, but responses have been observed in PD-L1-negative patients
  - Other predictive biomarkers should also be examined in OC
- Future approaches in anti-PD-1/PD-L1 treatment in upper GI cancers include:
  - Combination with VEGF pathway inhibitors; HER-2 directed therapy; CT ± RT
  - Combination with other immunotherapies that may overcome primary or acquired resistance to PD-1-directed therapy

4012: METGastric: A phase III study of onartuzumab plus mFOLFOX6 in patients with metastatic HER2-negative (HER2-) and MET-positive (MET+) adenocarcinoma of the stomach or gastroesophageal junction (GEC) – Shah MA, et al

Study objective

- To examine the efficacy and safety of onartuzumab + mFOLFOX6 compared with placebo + mFOLFOX6 in patients with HER2^{-} MET^{+} GEC

Key patient inclusion criteria

- HER2^{-}, MET^{+} (IHC* 1^{+}, 2^{+} or 3^{+}) GEC
- No prior treatment for metastatic disease
- Retained organ function
- ECOG PS 0–1

(n=563)

R 1:1

Onartuzumab (10 mg/kg) q2w + mFOLFOX6 (n=279) → PD

Stratification

- MET IHC status
- Geography
- Prior gastrectomy

Placebo q2w + mFOLFOX6 (n=283) → PD

PRIMARY ENDPOINTS

- OS (ITT population)
- OS (MET 2^{+}/3^{+} subgroup)

SECONDARY ENDPOINTS

- PFS, ORR, safety

*MET 1^{+}, 2^{+} or 3^{+} correlates with weak, moderate or strong staining, respectively

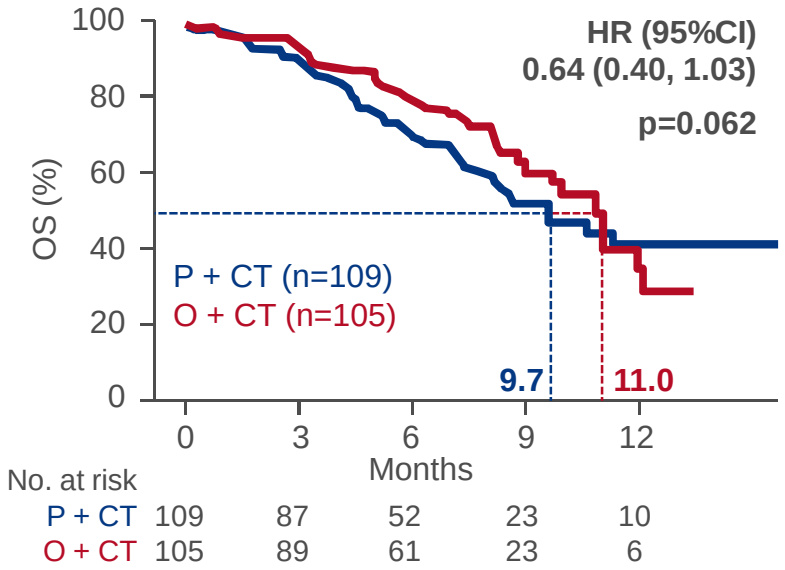
Shah et al. J Clin Oncol 2015; 33 (suppl): abstr 4012

4012: METGastric: A phase III study of onartuzumab plus mFOLFOX6 in patients with metastatic HER2-negative (HER2-) and MET-positive (MET+) adenocarcinoma of the stomach or gastroesophageal junction (GEC) – Shah MA, et al

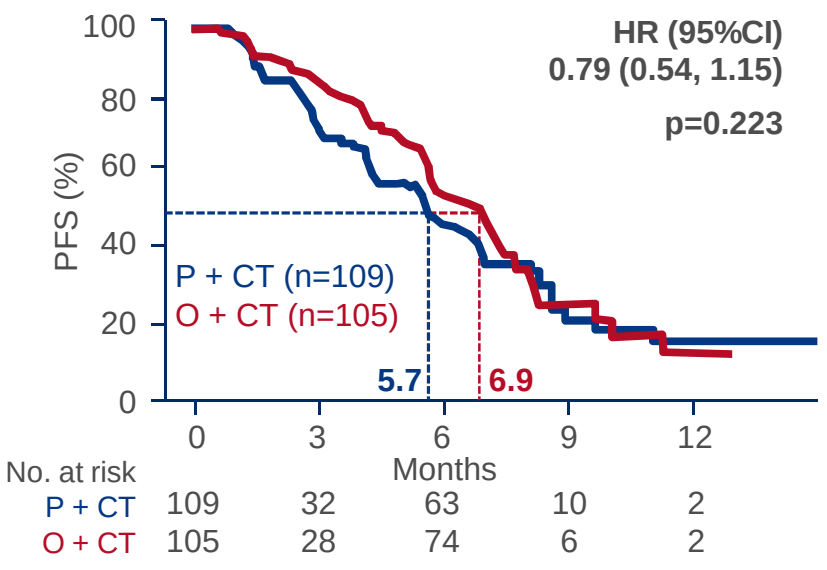
Key results

ITT population	O + CT (n=279)	P + CT (n=283)	HR (95%CI)	p-value
mOS, m	11.0	11.3	0.82 (0.59, 1.15)	0.24
mPFS, m	6.7	6.8	0.90 (0.71, 1.16)	0.429
ORR, %	46.1	40.6	-	0.253
DCR, %	78.3	73.9	-	-

OS MET 2+/3+ subgroup*



PFS MET 2+/3+ subgroup*



*Moderate or strong MET expression, respectively.
O, onartuzumab; P, placebo

Shah et al. J Clin Oncol 2015; 33 (suppl): abstr 4012

4012: METGastric: A phase III study of onartuzumab plus mFOLFOX6 in patients with metastatic HER2-negative (HER2-) and MET-positive (MET+) adenocarcinoma of the stomach or gastroesophageal junction (GEC) – Shah MA, et al

Key results (cont.)

- In the MET $2^+/3^+$ subgroups, ORR was 53.8 vs. 44.6% (p=0.228) for onartuzumab + mFOLFOX6 vs. placebo + mFOLFOX6, and DCR was 79.5 vs. 71.7%, respectively
- Sub-analysis in non-Asian patients with MET^+ GEC and no prior gastrectomy (n=125):
  - OS: 11.1 vs. 7.3 months (HR 0.51 [95%CI 0.29, 0.89]) for onartuzumab vs. placebo

AE, n (%)	Onartuzumab + mFOLFOX6	Placebo + mFOLFOX6
At least one AE	274 (98.2)	273 (97.5)
Grade 3–5 AE	192 (68.8)	187 (66.8)
Deaths	70 (25.1)	73 (26.1)
SAEs	100 (35.8)	91 (32.5)
AE leading to withdrawal	87 (31.2)	61 (21.8)

Conclusions

- **Onartuzumab + mFOLFOX6 did not improve survival vs. placebo + mFOLFOX6 in patients with $HER2^-$ MET^+ GEC; the safety profile was as expected for onartuzumab**
- **There was a trend for a clinical benefit in a MET^+ non-Asian subgroup without prior gastrectomy; suggesting a target population could still benefit from onartuzumab**

*Moderate or strong MET expression, respectively.
O, onartuzumab; P, placebo

Shah et al. J Clin Oncol 2015; 33 (suppl): abstr 4012

4013: FOLFOX alone or combined to rilotumumab or panitumumab as first-line treatment in patients (pts) with advanced gastroesophageal adenocarcinoma (AGEA): An open-label, randomized phase II trial (PRODIGE 17 ACCORD 20 MEGA) – Malka D, et al

Objective

- To investigate the efficacy and safety of FOLFOX alone and in combination with either rilotumumab or panitumumab in patients with advanced gastroesophageal adenocarcinoma

Key patient inclusion criteria
- Measurable advanced gastroesophageal adenocarcinoma
- Non-HER2$^+$
- ECOG PS 0–1

(n=162)

R

FOLFOX* + panitumumab 6 mg/kg q2w (n=49) → **PD or toxicity**

FOLFOX* + rilotumumab 10 mg/kg q2w (n=57) → **PD or toxicity**

FOLFOX* (n=56) → **PD or toxicity**

Stratification
- *Lauren classification*
- Disease stage
- Centre

PRIMARY ENDPOINT
- PFS

SECONDARY ENDPOINTS
- TTP, OS, safety

*Oxaliplatin 85 mg/m^2, folinic acid 400 mg/m^2, fluorouracil 400 mg/m^2 bolus then 2,400 mg/m^2 over 46 h

Malka et al. J Clin Oncol 2015; 33 (suppl): abstr 4013

4013: FOLFOX alone or combined to rilotumumab or panitumumab as first-line treatment in patients (pts) with advanced gastroesophageal adenocarcinoma (AGEA): An open-label, randomized phase II trial (PRODIGE 17 ACCORD 20 MEGA) – Malka D, et al

Key results

	FOLFOX + panitumumab (n=49)	FOLFOX + rilotumumab (n=57)	FOLFOX (n=56)
PFS at 4 months, % (95%CI)	63 (48, 75)	63 (49, 74)	71 (57, 81)
TTP, months (range)	5.7 (4.3, 7.9)	7.8 (5.6, 9.9)	5.9 (5.5, 7.4)
Median PFS, months (range)	5.2 (3.7, 7.6)	7.6 (4.0, 9.0)	5.8 (5.2, 7.3)
Median OS, months (range)	8.3 (6.2, 13.2)	11.5 (7.9, 17.1)	13.1 (8.7, 16.9)

AEs, %	FOLFOX + panitumumab (n=49)	FOLFOX + rilotumumab (n=57)	FOLFOX (n=56)
Grade ≥3 AEs	83	90	62
Peripheral neuropathy	6	33	17
Neutropenia (febrile)	27 (8)	28 (5)	26 (0)
Asthenia	17	14	6
Diarrhoea	15	2	4
Anaemia	10	5	4
Vomiting	10	4	4
Rash	10	2	2

Conclusions

- PFS was reached in all treatment groups
- Combining FOLFOX with either panitumumab or rilotumumab appeared to cause more toxicity and was not associated with greater efficacy

Malka et al. J Clin Oncol 2015; 33 (suppl): abstr 4013

4014: A randomized, open-label phase II study of AZD4547 (AZD) versus paclitaxel (P) in previously treated patients with advanced gastric cancer (AGC) with fibroblast growth factor receptor 2 (FGFR2) polysomy or gene amplification (amp): SHINE study – Bang Y, et al

Objective

- To investigate the efficacy and safety of the AZD4547 (a selective inhibitor of the FGFR1, 2 and 3 tyrosine kinases) in patients with advanced gastric cancer

Key patient inclusion criteria
- Advanced gastric cancer
- PD after first-line therapy
- *FGFR2* amplified or polysomy†

(n=71)

R

Oral AZD4547* (n=41) → PD

Stratification (by *FGFR2* status†)
- Polysomy (FISH4/5, ratio <2.0 and ≥4 copies in ≥10% of cells)
- Low amplification (FISH6, ratio >2.0)
- High amplification (FISH6, ratio ≥5.0)

Paclitaxel‡ (n=30) → PD

PRIMARY ENDPOINT
- PFS, safety

SECONDARY ENDPOINT
- OS, ORR, DOR, quality of life

*80 mg bid 2 weeks on, 1 week off q3w;
‡80 mg/m^2 IV, D1, 8 and 15 q4w
†Determined by FISH testing

Bang et al. J Clin Oncol 2015; 33 (suppl): abstr 4014

4014: A randomized, open-label phase II study of AZD4547 (AZD) versus paclitaxel (P) in previously treated patients with advanced gastric cancer (AGC) with fibroblast growth factor receptor 2 (FGFR2) polysomy or gene amplification (amp): SHINE study – Bang Y, et al

Key results

- The prevalence of *FGFR2* amplification was 9%

mPFS, months	AZD4547	Paclitaxel	HR (80%CI)
Overall	1.8	3.5	1.57 (1.12, 2.21)
FGFR2-amplified group	1.5	2.3	1.30 (0.81, 2.12)

- Grade 3/4 AEs occurred in 35.0 vs. 44.4% for AZD4547 vs. paclitaxel and AEs leading to discontinuation in 5.0 vs. 7.4%, respectively
- Elevations in plasma phosphate were observed in the AZD4547 arm
- Only 21% of *FGFR2*-amplified tumours had elevated *FGFR2* expression
  - 4 of 7 tumours (highly amplified by FISH) were amplified in <20% of the tumour section

Conclusions

- **AZD4547 did not improve PFS vs. paclitaxel in patients with *FGFR2*-amplified or polysomy advanced gastric cancer but was well tolerated**
- **The observed increases in plasma phosphate provides evidence that AZD4547 causes pharmacological target inhibition at this dose**

Bang et al. J Clin Oncol 2015; 33 (suppl): abstr 4014

4015: Untreated metastatic diffuse gastric adenocarcinoma (DGAC): Randomized phase III study of S-1 and cisplatin vs. 5-FU and cisplatin (the DIGEST trial) – Ajani JA, et al

Objective

- To investigate efficacy and safety of first-line S-1 + cisplatin vs. 5FU + cisplatin in patients with previously untreated metastatic DGAC

Key patient inclusion criteria

- Metastatic DGAC
- No prior chemotherapy
- ECOG PS 0–1

(n=361)

R 2:1

S-1* + cisplatin
75 mg/m^2 D1 q4w
(n=239)

→ PD

Stratification

- Histological subtype
- Extent of metastases
- ECOG PS
- Region

5FU† + cisplatin
80 mg/m^2 D1 q3w
(n=122)

→ PD

PRIMARY ENDPOINT(S)

- OS

SECONDARY ENDPOINTS

- PFS, TTF, ORR, safety

- The study was stopped early (initial target was 500 patients)

*25 mg/m^2 bid D1–21; †800 mg D1–5

Ajani et al. J Clin Oncol 2015; 33 (suppl): abstr 4015

4015: Untreated metastatic diffuse gastric adenocarcinoma (DGAC): Randomized phase III study of S-1 and cisplatin vs. 5-FU and cisplatin (the DIGEST trial) – Ajani JA, et al

Key results

	S-1 + cisplatin (n=239)	5FU + cisplatin (n=122)	HR (95%CI)	p-value
mOS, months	7.5	6.6	0.99 (0.76, 1.28)	0.93
mPFS, months	4.4	3.9	0.86 (0.65, 1.14)	0.30
CR + PR	34.7	19.8		0.01
CR	0.5	0.0	-	-
PR	34.2	19.8		
SD	30.1	34.1	-	-
Not evaluable	22.3	28.6		

Grade 3 AEs (occurring in >5%), %	S-1 + cisplatin (n=239)	5FU + cisplatin (n=122)
Any	68.3	66.1
Decreased appetite	3.9	5.9
Fatigue	10.4	4.2
Asthenia	5.7	10.2
Abdominal pain	5.7	1.7

Conclusion

- S1 + cisplatin did not prolong OS vs. 5FU + cisplatin in patients with metastatic DGAC
  - Efficacy and safety were similar between the two treatment groups

Ajani et al. J Clin Oncol 2015; 33 (suppl): abstr 4015

Gastroesophageal cancers: Finding the right targets – Iqbal S

Discussion of abstract 4012

- No significant difference in OS or PFS with the addition of onartuzumab to CT
  - There was a non-significant trend towards improved survival in MET $2^+/3^+$ patients
- Was there enough data to support an RCT?
  - Data based on a phase 1 trial in which one patient achieved CR
- What is optimal patient selection for targeting MET pathway
  - The majority of studies evaluate MET using IHC
    - Protein expression does not always measure activation of the pathway
    - Antibody kits vary widely
    - FISH amplification has been reported in 5–10% of patients with gastric cancer but has not been examined yet with onartuzumab
- Do we continue to investigate the MET pathway after three negative trials?
  - Robust biomarker re-evaluation is needed before perusing any further studies
  - Could consider multi-targeted therapies
- Take home message:
  - No further trials with MET inhibition with the current selection biomarker
- Next steps
  - 'Bucket trials' (where patients are recruited via biomarker status rather than cancer type) of limited size to identify biomarkers, assessing several agents then selecting the most appropriate treatment and evaluating more rigorously

Gastroesophageal cancers: Finding the right targets – Iqbal S

Discussion of abstract 4015

- A phase 3 trial in DGAC initiated based on retrospective subgroup analysis
- Study stopped early due to lack of benefit between the two treatment arms
- Should we continue to study S-1 in a Western population?
  - This was a subgroup analysis with no molecular characteristics evaluated
  - S-1 has not demonstrated superiority over 5FU and in the US the standard of care remains 5FU + capecitabine
  - Future investigation for fluoropyrimidines should be driven by biology
- How can trial design be improved?
  - Preclinical work should continue to identify relevant pathways and biomarkers
  - Phase 1 (with expansion cohorts), with serial biopsies and biomarker validation
  - Randomised phase 2 studies to continue to validate biomarker with demonstrable efficacy
  - Phase 3 trials with aggressive stopping rules to ensure patients are not accrued to negative studies
- Take home message:
  - S-1 equivalent to 5FU

NEUROENDOCRINE TUMOURS

4004: SWOG S0518: Phase III prospective randomized comparison of depot octreotide plus interferon alpha-2b versus depot octreotide plus bevacizumab (NSC #704865) in advanced, poor prognosis carcinoid patients (NCT00569127) – Yao JC, et al

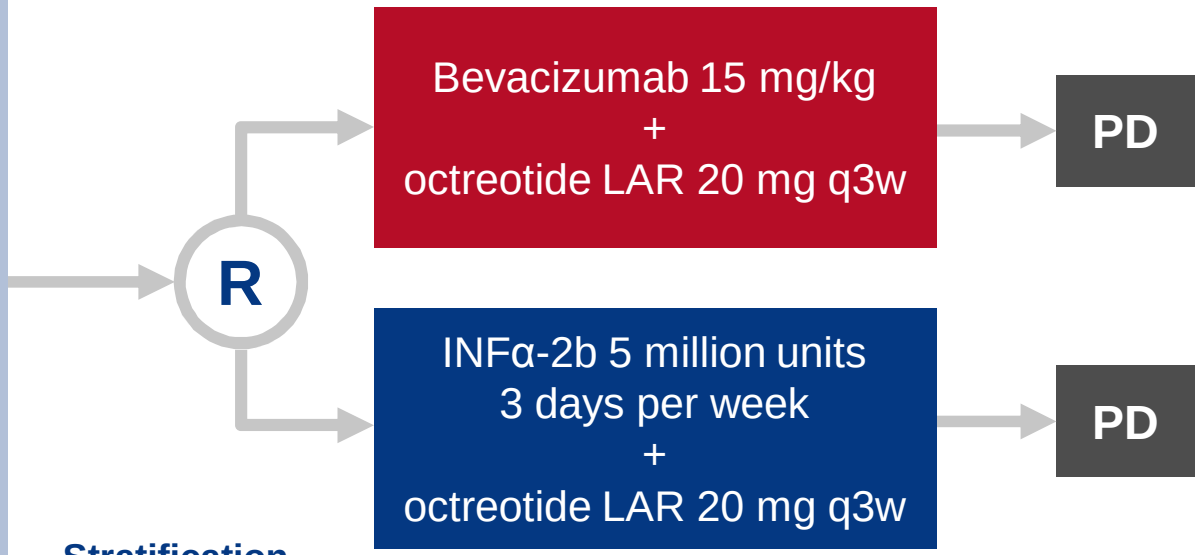
Study objective

- To compare the antitumour activity of bevacizumab plus octreotide with INFα-2b plus octreotide in patients with advanced carcinoid neuroendocrine tumours (NETs)

Key patient inclusion criteria

- Unresectable metastatic or locally advanced, well-differentiated G1/2 NETs with progressive disease
- G2 with 6+ lesion
- Colorectal or gastric primary
- Up to one prior cytotoxic chemotherapy

(n=402)



Stratification

- Primary site (midgut vs. others)
- RECIST PD since diagnosis
- Histologic grade (G1 vs. G2)
- Octreotide 2 months prior to registration

PRIMARY ENDPOINT

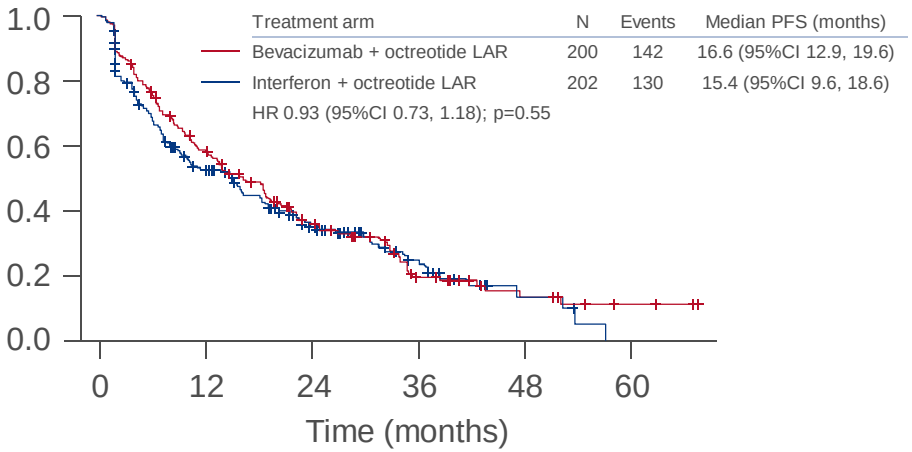
- PFS by central review

Yao et al. J Clin Oncol 2015; 33 (suppl): abstr 4004

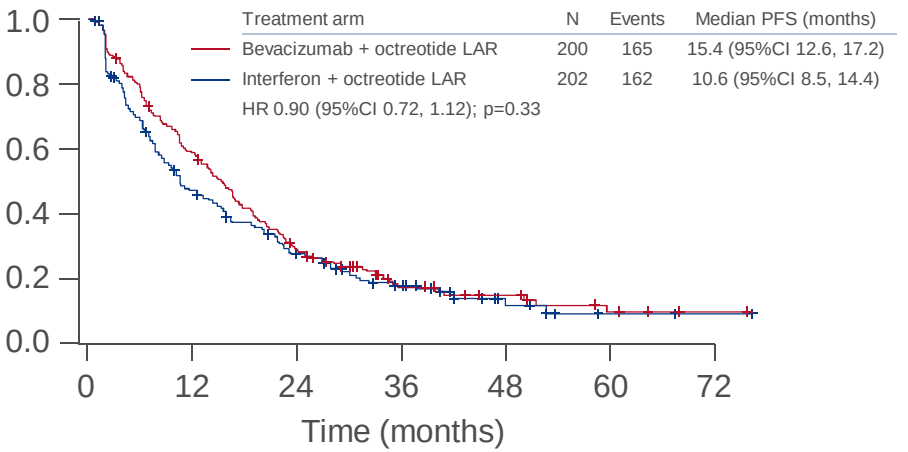
4004: SWOG S0518: Phase III prospective randomized comparison of depot octreotide plus interferon alpha-2b versus depot octreotide plus bevacizumab (NSC #704865) in advanced, poor prognosis carcinoid patients (NCT00569127) – Yao JC, et al

Key results

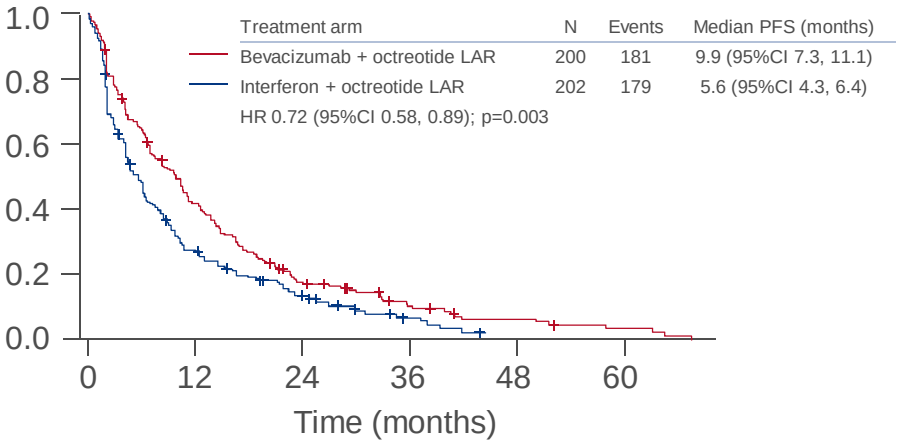
PFS by central review



PFS by investigator review



Time to treatment failure



Yao et al. J Clin Oncol 2015; 33 (suppl): abstr 4004

4004: SWOG S0518: Phase III prospective randomized comparison of depot octreotide plus interferon alpha-2b versus depot octreotide plus bevacizumab (NSC #704865) in advanced, poor prognosis carcinoid patients (NCT00569127) – Yao JC, et al

Key results (cont.)

CTCAE v3.0 (occurring in ≥5%)	Bevacizumab + octreotide LAR (n=197)		IFNα-2b + octreotide LAR (n=194)	
	All Grades, n (%)	Grade ≥3, n (%)	All Grades, n (%)	Grade ≥3, n (%)
Hypertension	63 (32.0)	62 (31.5)	4 (2.1)	4 (2.1)
Fatigue	14 (7.1)	13 (6.6)	52 (26.8)	50 (25.8)
Neutrophils	0 (0.0)	0 (0.0)	23 (11.9)	23 (11.9)
Proteinuria	17 (8.6)	17 (8.6)	1 (0.5)	1 (0.5)
Leukocytes	4 (2.0)	2 (1.0)	14 (7.2)	14 (7.2)
Nausea	6 (3.0)	5 (2.5)	11 (5.7)	9 (4.6)
Headache	10 (5.1)	9 (4.6)	4 (2.1)	3 (1.5)
Diarrhoea	9 (4.6)	7 (3.6)	9 (4.6)	9 (4.6)

Conclusion

- **No significant differences in PFS were observed between the two treatments. However, bevacizumab + ocreotide was associated with a longer time to treatment failure than IFNα-2b + ocreotide but less fatigue and neutropenia**

Yao et al. J Clin Oncol 2015; 33 (suppl): abstr 4004

4005: Randomized phase II study of everolimus (E) versus everolimus plus bevacizumab (E+B) in patients (pts) with locally advanced or metastatic pancreatic neuroendocrine tumors (pNET), CALGB 80701 (Alliance) – Kulke MH, et al

Study objective

- To evaluate the efficacy and safety of everolimus + bevacizumab in patients with advanced pNET

Key patient inclusion criteria

- Advanced pancreatic NET
- PD within 12 months
- No prior bevacizumab or mTOR inhibitor

(n=150)

R 1:1

Everolimus 10 mg/day po + bevacizumab 10 mg/kg IV q2w (n=75) → PD

Stratification

- Prior somatostatin analogues
- Prior cytotoxic CT
- Prior sunitinib

Everolimus 10 mg/day po (n=75) → PD

PRIMARY ENDPOINT

- PFS

SECONDARY ENDPOINTS

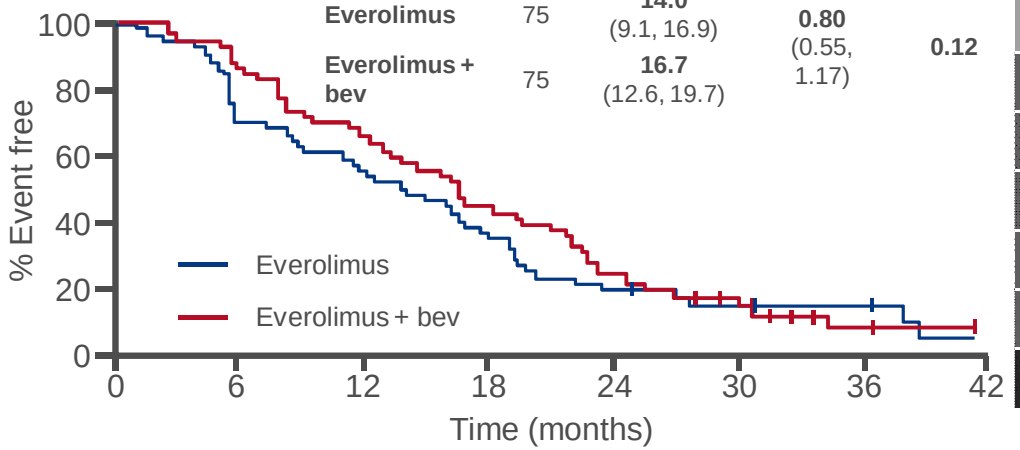
- OS, RR and safety

Kulke et al. J Clin Oncol 2015; 33 (suppl): abstr 4005

4005: Randomized phase II study of everolimus (E) versus everolimus plus bevacizumab (E+B) in patients (Pts) with locally advanced or metastatic pancreatic neuroendocrine tumors (pNET), CALGB 80701 (Alliance) – Kulke MH, et al

Key results

PFS



Arm	N	Median PFS, months (95%CI)	HR (95%CI)	p-value
Everolimus	75	**14.0** (9.1, 16.9)	**0.80** (0.55, 1.17)	**0.12**
Everolimus + bev	75	**16.7** (12.6, 19.7)		

	Everolimus	Everolimus + bevacizumab
ORR, %	12	31
p-value	0.005	
mOS, months	35.0	36.7
HR (95%CI); p-value	0.72 (0.4, 1.28); 0.13	
mTTF, months	12.2	12.6
HR (95%CI); p-value	0.95 (0.66, 1.37); 0.39	

- Any grade 3/4 AEs (everolimus vs. everolimus + bevacizumab): 49 vs. 81%
  - Most common (≥10%) were: hypertension (8 vs. 38%); hyperglycaemia (12 vs. 14%); proteinuria (1 vs. 16%); diarrhoea (1 vs. 11%); and hypophosphatemia (1 vs. 10%)

Conclusions

- **Everolimus + bevacizumab was associated with superior RR vs. everolimus alone and a trend towards prolonged PFS in patients with advanced pNET**
- **Despite being associated with more AEs, everolimus + bevacizumab is clearly feasible and regimens combining mTOR + VEGF inhibitors warrant further study**

Kulke et al. J Clin Oncol 2015; 33 (suppl): abstr 4005

Targeting angiogenic and other molecular pathways in neuroendocrine tumors – Reidy DL

Discussion of abstract 4004

- IFNα is associated with severe side effects and is not a standard therapy in the US
  - For better tolerability, pegylated IFN was used in this trial
- The study was negative: PFS was similar with bevacizumab vs. IFN
  - ORR was higher with bevacizumab vs. IFN
  - Grade 3 fatigue was higher and TTF was shorter with IFN vs. bevacizumab
- The study protocol was amended due to low event rates, reflecting NET heterogeneity
- In addition, it is questionable whether this was truly a poor prognosis patient population
  - 85% of patients had G1 tumours
- PFS was high in both arms (16.6 months bevacizumab vs. 15.4 months with IFN)
  - Does this reflect that both treatments worked?

Conclusions

- **Single agent pegylated IFN is toxic with unknown efficacy**
- **Single agent bevacizumab is tolerable with unknown efficacy**
- **Based on these data, neither bevacizumab nor IFN should not be used as a standard treatment in NET**
- **However, other VEGF trials should be considered and are currently ongoing**

Targeting angiogenic and other molecular pathways in neuroendocrine tumors – Reidy DL

Discussion of abstract 4005

- Everolimus + bevacizumab was associated with superior efficacy vs. everolimus alone
  - However, grade 3/4 toxicities were higher with combination therapy vs. monotherapy
- VEGF + mTOR inhibitor has proven benefit when used *sequentially* in renal cell carcinoma, but combination therapy was highly toxic when used in combination therapy
- A phase 2 study in pNET[1] (n=22) demonstrated reasonable efficacy (PFS 18 months, ORR 14%) with bevacizumab monotherapy and no grade 3/4 toxicities
  - This study suggests that sequential therapy may be beneficial
- NET treatment and management
  - Appropriate treatment selection depends on clinical judgement
    - Careful observation is appropriate for asymptomatic low grade tumours
    - Symptomatic patients with high burden should be treated ASAP

Conclusions

- **ORR was 31% with dual therapy, which was a paradigm shift for NET**
- **Sequential therapy should be investigated for VEGF ± mTOR inhibition**
- **Phase 2 data should be interpreted with caution: toxicity may outweigh benefits**
- **Phase 3 data are needed to assess toxicity and confirm efficacy**

1. Hobday et al. J Clin Oncol 2015; 33 (suppl): abstr 4096

PANCREATIC CANCER

4007: CONKO-005: Adjuvant therapy in R0 resected pancreatic cancer patients with gemcitabine plus erlotinib versus gemcitabine for 24 weeks—A prospective randomized phase III study – Sinn M, et al

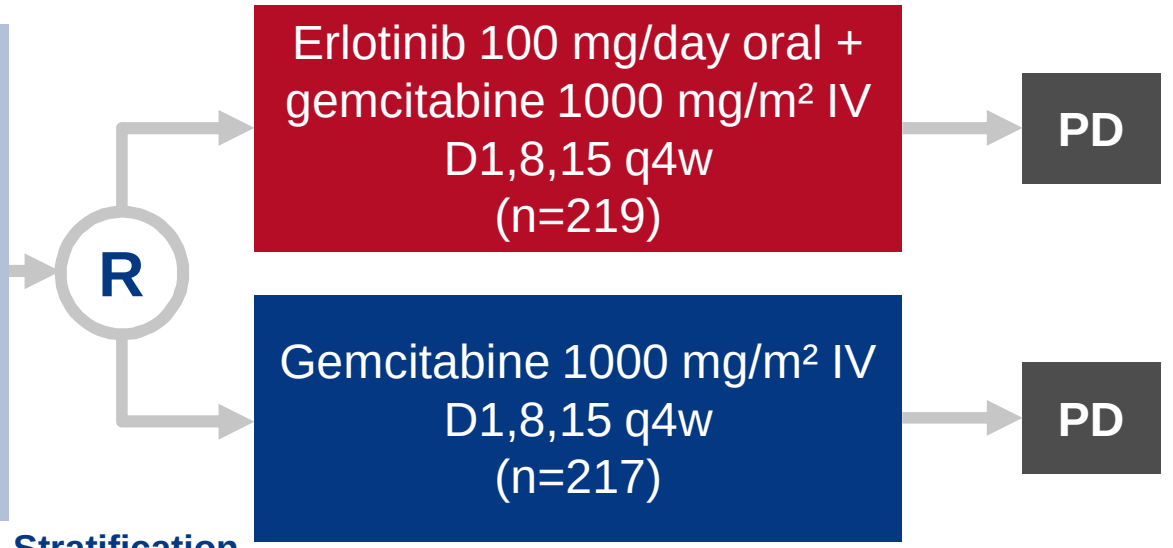
Study objective

- To asses the additional effect of the EGFR TKI erlotinib in combination with gemcitabine for 24 weeks in patients with pancreatic cancer after R0 resection

Key patient inclusion criteria

- Histologically confirmed adenocarcinoma, R0 resected
- Treatment naïve
- KPS ≥60% post-operative

(n=436)



Stratification

- Lymph node involvement (N+ vs. N0)
- Surgery
- T size
- KPS

PRIMARY ENDPOINT

- DFS

SECONDARY ENDPOINT

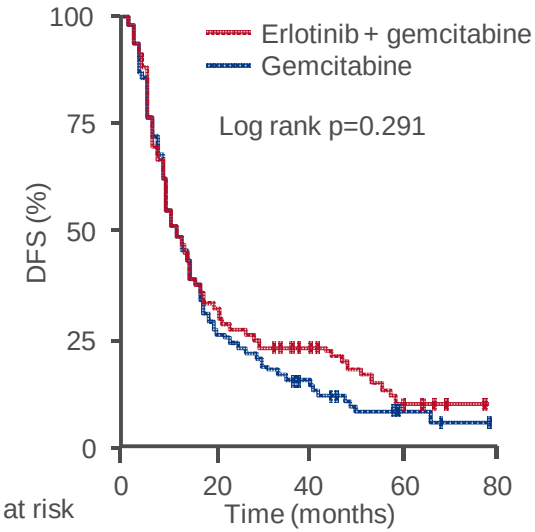
- OS, toxicity

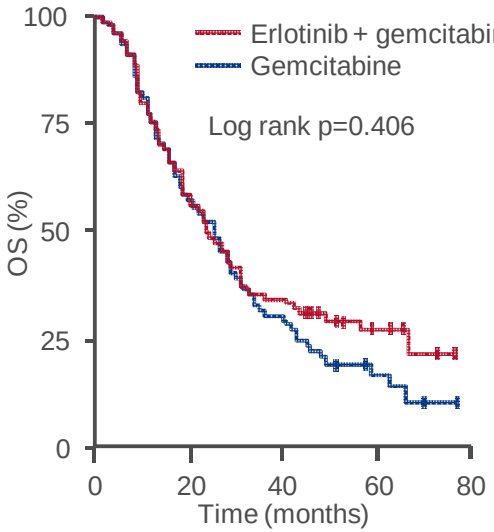
Sinn et al. J Clin Oncol 2015; 33 (suppl): abstr 4007

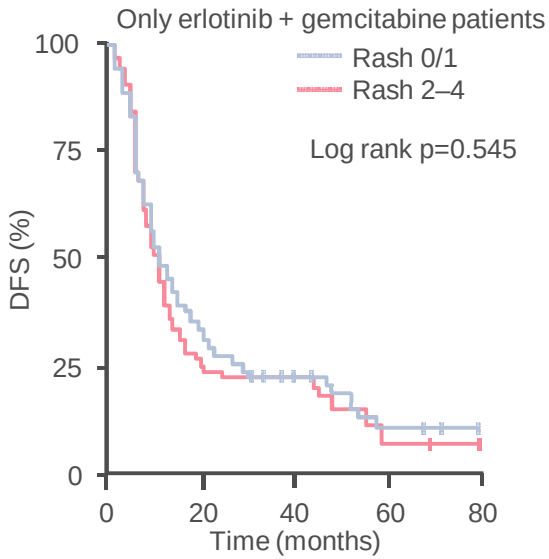
4007: CONKO-005: Adjuvant therapy in R0 resected pancreatic cancer patients with gemcitabine plus erlotinib versus gemcitabine for 24 weeks—A prospective randomized phase III study – Sinn M, et al

Key results

- There was no difference between the two groups in median DFS (both 11.6 months) or OS (24.6 vs. 26.5 months for erlotinib + gemcitabine vs. gemcitabine)
- There was no correlation between the grade of rash and an improved DFS with erlotinib + gemcitabine







No. at risk					
Erlotinib + gemcitabine	219	65	31	6	0
Gemcitabine	217	155	16	4	0

	219	120	39	12	0
	217	119	32	9	0

Rash 0/1	133	45	16	4	0
Rash 2–4	75	19	14	2	0

Conclusion

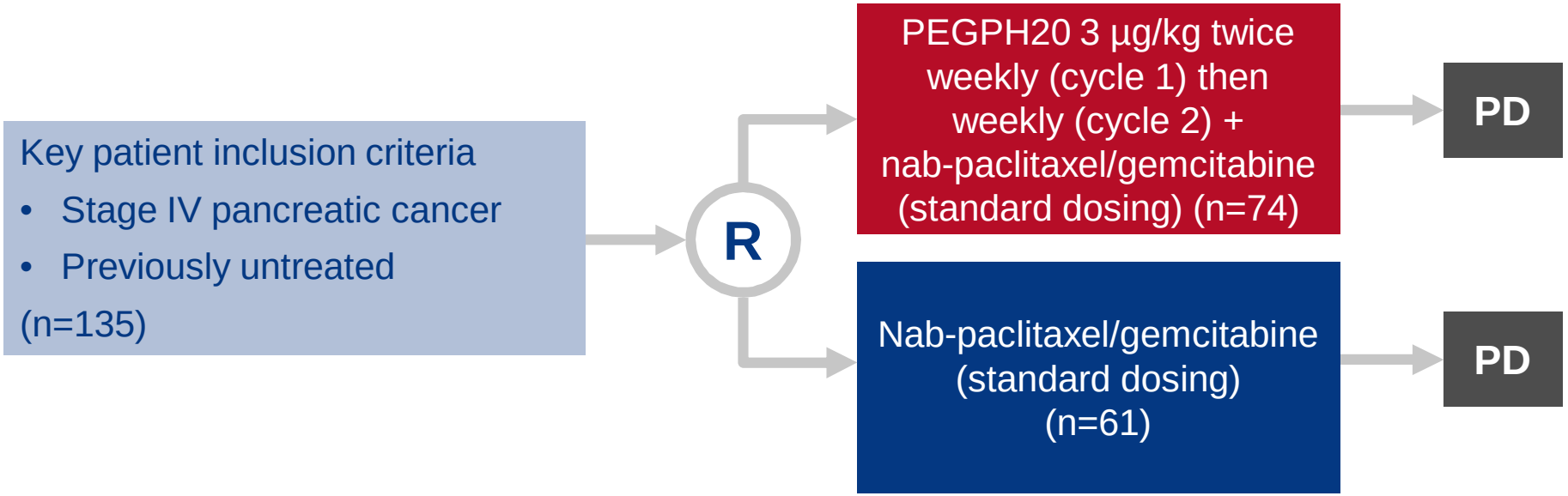
- **Addition of erlotinib to gemcitabine for 24 weeks did not improve DFS or OS. There was a trend in favour of long-term survival in patients receiving erlotinib + gemcitabine**

Sinn et al. J Clin Oncol 2015; 33 (suppl): abstr 4007

4006: High response rate and PFS with PEGPH20 added to nab-paclitaxel/ gemcitabine in stage IV previously untreated pancreatic cancer patients with high-HA tumors: Interim results of a randomized phase II study – Hingorani SR, et al

Study objective

- To determine efficacy and safety of PEGPH20 + nab-paclitaxel/gemcitabine (PAG) compared with nab-paclitaxel/gemcitabine alone in pancreatic cancer



- Hyaluronan (HA) status tested retrospectively

PRIMARY ENDPOINT

- PFS

SECONDARY ENDPOINT

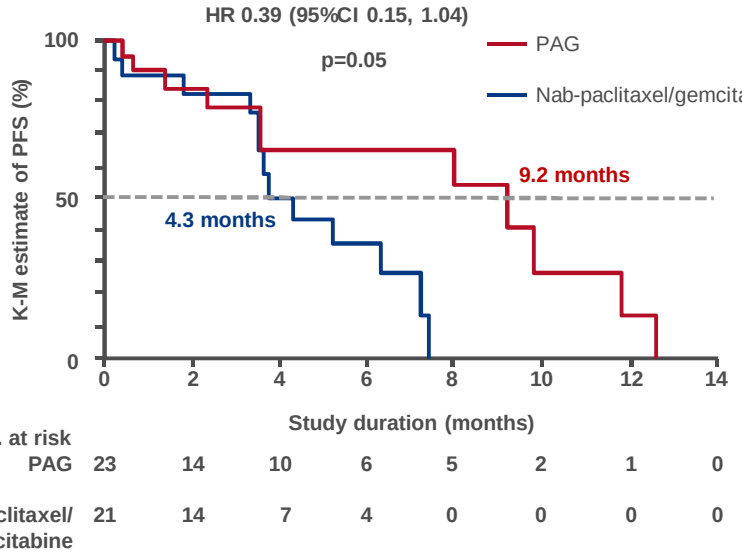
- PFS by HA level, ORR, OS, safety

Hingorani et al. J Clin Oncol 2015; 33 (suppl): abstr 4006

4006: High response rate and PFS with PEGPH20 added to nab-paclitaxel/gemcitabine in stage IV previously untreated pancreatic cancer patients with high-HA tumors: Interim results of a randomized phase II study – Hingorani SR, et al

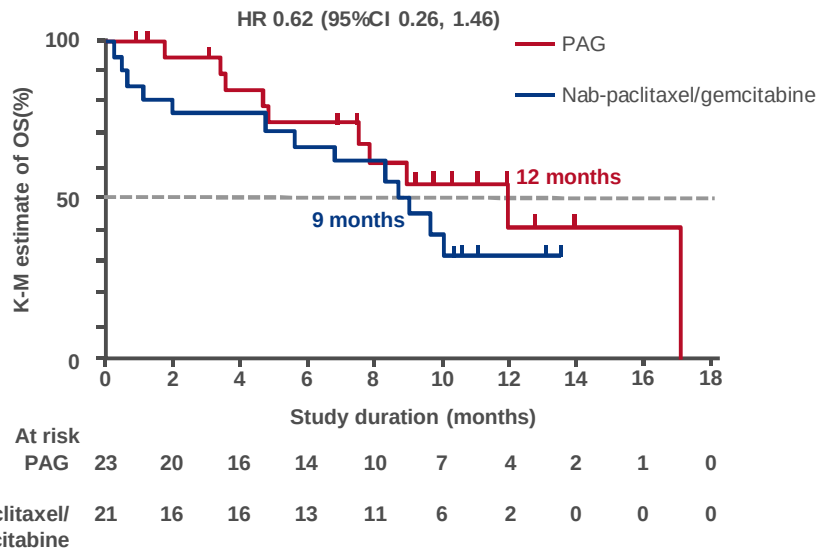
Key results

PFS in HA-high patients



No. at risk								
PAG	23	14	10	6	5	2	1	0
Nab-paclitaxel/ gemcitabine	21	14	7	4	0	0	0	0

OS in HA-high patients



At risk										
PAG	23	20	16	14	10	7	4	2	1	0
Nab-paclitaxel/ gemcitabine	21	16	16	13	11	6	2	0	0	0

Hingorani et al. J Clin Oncol 2015; 33 (suppl): abstr 4006

4006: High response rate and PFS with PEGPH20 added to nab-paclitaxel/gemcitabine in stage IV previously untreated pancreatic cancer patients with high-HA tumors: Interim results of a randomized phase II study – Hingorani SR, et al

Key results (cont.)

- ORR in PAG and nab-paclitaxel/gemcitabine groups was 73% and 27%, respectively

Endpoint/Population	PAG	Nab-paclitaxel/gemcitabine	p-value
Events/total (n); median PFS (months)			
All treated population	42/74; 5.7	39/61; 5.2	0.11
All treated population with HA data	34/61; 5.5	30/45; 4.8	0.09
High HA	11/23; 9.2	13/21; 4.3	0.05
Low HA	23/38; 5.3	17/24; 5.6	0.74
Responders/total (n) [%]; duration (months)			
All treated population	30/74 [41]; 7.4	21/61 [34]; 4.2	0.48
All treated population with HA data	26/61 [43]; 8.1	14/45 [3.1; 4.2	0.22
High HA	12/23 [52]; 8.1	5/17 [24]; 3.7	0.038
Low HA	14/38 [37]; 5.8	9/24 [38]; 4.8	0.96

Most common AEs (occurring in >50% of any grade), n (%)	PAG (n=74)		Nab-paclitaxel/gemcitabine (n=61)	
	Any Grade	Grade 3+	Any Grade	Grade 3+
Fatigue	50 (67.6)	13 (17.6)	42 (68.9)	11 (18.0)
Nausea	41 (55.4)	5 (6.8)	27 (44.3)	2 (3.3)
Anaemia	31 (41.9)	14 (18.9)	32 (52.5)	10 (16.4)
Peripheral oedema	43 (58.1)	2 (2.7)	19 (31.1)	4 (6.6)
Muscle spasms	41 (55.4)	6 (8.1)	1 (1.6)	0

Conclusion

- **PFS and ORR were greater in patients with high HA levels receiving PEGPH20 + nab-paclitaxel/gemcitabine than in those receiving nab-paclitaxel/gemcitabine**

Hingorani et al. J Clin Oncol 2015; 33 (suppl): abstr 4006

Pancreatic cancer: The current state and future of research – Yu KH

Discussion of abstract 4007

- Erlotinib + gemcitabine did not result in a survival benefit
- Erlotinib was not active in the adjuvant setting
- Current approaches in pancreatic cancer are focused on regimens that are active in the advanced disease setting
- Future approaches will leverage tissues and molecular tools

Discussion of abstract 4006

- HA^{high} levels appeared to predict response with PEGH20; no PFS benefit in HA^{low} patients
- There was a preliminary OS benefit with PEGH20 vs. CT alone (12 vs. 9 months)
- PEGH20 was generally well tolerated, with an increase in thromboembolic event
- Future studies could potentially look at PEGH2 + other cytotoxic CT agents in multiple arms of therapy or in an earlier stage of disease

Conclusion

- **A promising new tumour microenvironment-directed therapy; we await the results of a planned RCT**

4021: Quantification of tumor stroma as a biomarker in pancreatic adenocarcinoma – Torphy RJ, et al

Study objective

- To evaluate the prognostic significance of the abundance of tumour stroma, inflammatory infiltrate, nerves and blood vessels in resected primary pancreatic ductal adenocarcinoma (PDAC)

Study design

- Sections from primary tumours of 106 patients who underwent curative pancreaticoduodenectomies without adjuvant therapy and 69 primary and metastatic tumours of 13 patients with metastatic PDAC were H&E stained and tumour epithelium, tumour stroma, inflammatory infiltrate, nerves and blood vessels were digitally annotated
- Tumour stroma density (TSD) was calculated using the following formula:

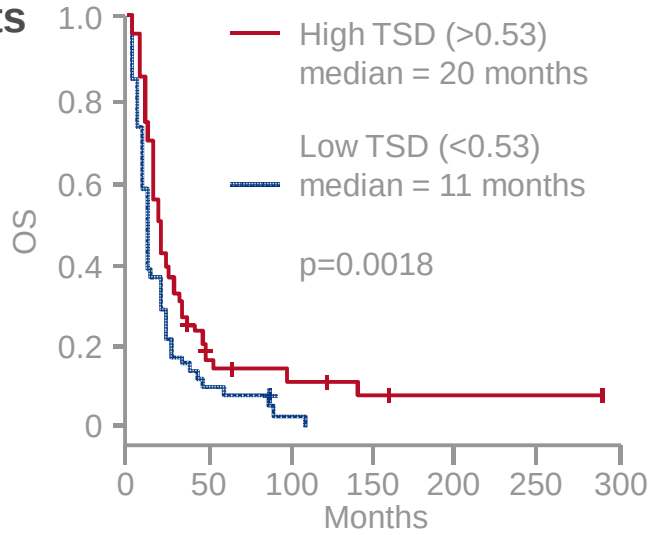
$$\text{Tumour stroma density} = \frac{\text{Tumour stroma area}}{\text{Total tumour area}}$$

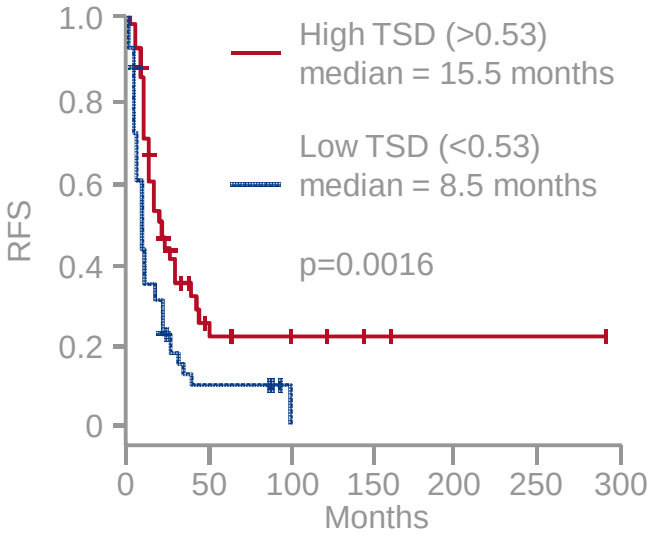
- OS and RFS were measured using the multivariate Cox proportional hazards model
- Tumour epithelium cellularity was quantified using Spectrum Webscope and compared with genomic data on tumour cellularity from The Cancer Genome Atlas (TCGA)

Torphy et al. J Clin Oncol 2015; 33 (suppl): abstr 4021

4021: Quantification of tumor stroma as a biomarker in pancreatic adenocarcinoma – Torphy RJ, et al

Key results





- High inflammatory infiltrate density was associated with a longer OS (p=0.0479), with median OS of 11 and 22 months in low and high inflammatory density groups, respectively
- There was no significant association with OS or RFS in nerve or blood vessel density
- There were no significant changes in tumour cellularity between the study samples and the TCGA

Conclusion

- **Tumour stroma was associated with restraining tumour growth with decreasing TSD in patients with more aggressive disease suggesting a role for using TSD to assess tumour stroma in correlative and therapeutic in trials of patients with PDAC**

Torphy et al. J Clin Oncol 2015; 33 (suppl): abstr 4021

4022: Prognostic value of plasma circulating tumor (ct) DNA *KRAS* mutations and serum CA19-9 in unresectable pancreatic cancer (PC) patients – Johansen JS, et al

Objective

- To investigate the prognostic value of *KRAS* mutation load ± serum CA19-9 in patients with unresectable pancreatic cancer receiving palliative CT

Study design

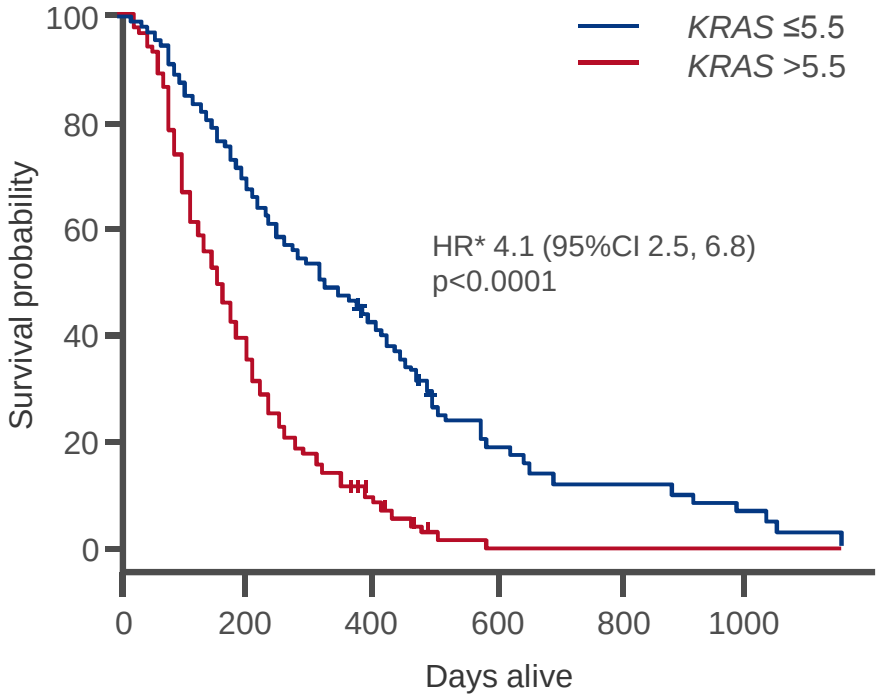
- Prospective biomarker study* analysing 640 archived plasma samples from 182 patients with non-resectable, locally advanced or metastatic pancreatic cancer undergoing treatment with CT
  - Patients received gemcitabine (n=151) or FOLFIRINOX (n=31)
- ctDNA *KRAS* codon 12/13 mutation levels were assessed at baseline and after CT to determine the association with OS
  - *KRAS* mutation levels were detected using quantitative mutation enrichment PCR-NGS assays in highly fragmented plasma ctDNA

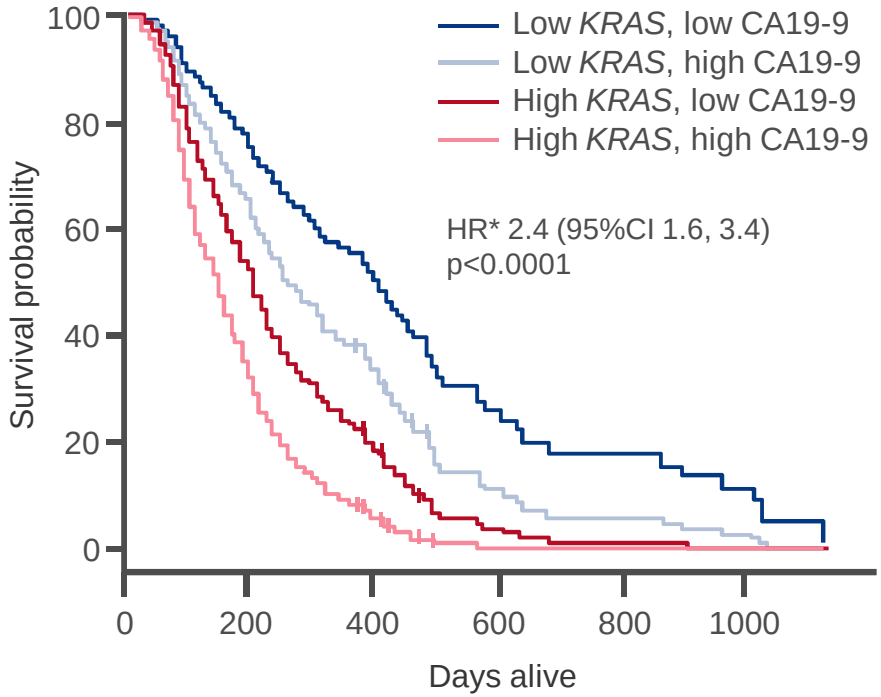
*Danish BIOPAC. CA19-9, carbohydrate antigen 19-9; ctDNA, circulating tumour DNA; PCR-NGS, polymerase chain reaction next generation sequencing

Johansen et al. J Clin Oncol 2015; 33 (suppl): abstr 4022

4022: Prognostic value of plasma circulating tumor (ct) DNA *KRAS* mutations and serum CA19-9 in unresectable pancreatic cancer (PC) patients – Johansen JS, et al

Key results





Conclusions

- **High baseline ctDNA *KRAS* levels were significantly associated with poor OS in patients with unresectable pancreatic cancer receiving palliative CT**
- ***KRAS* + CA19-9 combined had greater prognostic value than either marker alone**

*HR of death for high vs. low *KRAS* ± CA19-9

Johansen et al. J Clin Oncol 2015; 33 (suppl): abstr 4022

4023: Allelic ratio of *KRAS* mutations in pancreatic ductal adenocarcinoma – Lennerz JK, et al

Study objective

- To explore whether there are prognostic differences in pancreatic ductal adenocarcinoma (PDAC) that have *KRAS* mutations (which compose ~93% of all PDAC cases and are associated with shorter OS) at low allelic ratios

Study design

- The PDAC dataset (n=142) from the International Cancer Genome Consortium (ICGC) was used to identify *KRAS* mutations in PDAC tumours
- Tumour purity was accounted for by calculating the corrected allelic ratio (= allelic ratio/cellularity)
- Survival differences were calculated using a corrected allelic ratio cut-off of 10%

Key results

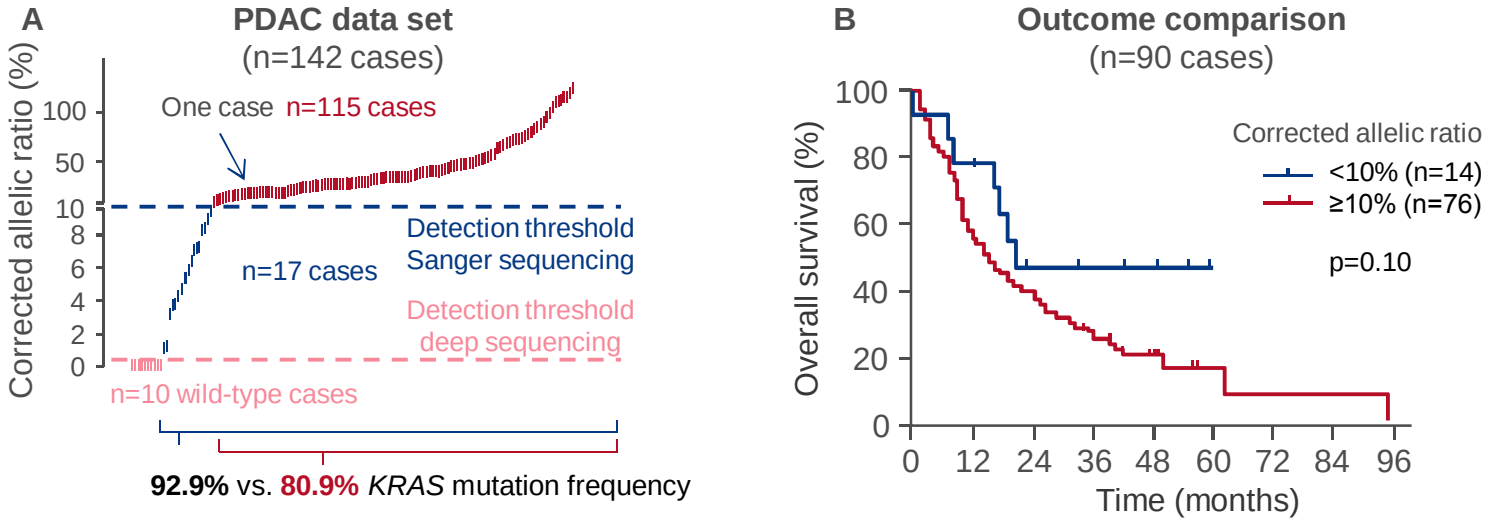
- 115 (80.9%) cases were identified with allelic ratios of mutant *KRAS* ≥10%
- Allelic ratios span from wild-type to 100% mutant suggesting heterogeneity within the cancer cell population (clonality) or variations in DNA content (ploidy)

Lennerz et al. J Clin Oncol 2015; 33 (suppl): abstr 4023

4023: Allelic ratio of KRAS mutations in pancreatic ductal adenocarcinoma – Lennerz JK, et al

Key results (cont.)

KRAS mutations in PDAC: allelic ratio (A) and overall survival (B)



- OS in the subset of PDAC with low allelic ratios (<10%) of mutant *KRAS* was 14.5 vs. 20.3 months in tumours with high allelic ratios (HR 1.68 [95%CI 0.9, 3.13]; p=0.10)

Conclusions

- *KRAS*-mutated tumours are heterogeneous suggesting that PDAC biology may vary with the tumour-specific allelic ratio and level of mutated *KRAS*
- When developing a comprehensive molecular diagnostic report, the tumour-specific allelic ratio of somatically mutated genes should be included

Lennerz et al. J Clin Oncol 2015; 33 (suppl): abstr 4023

Outside of the proverbial box: Molecular and cellular heterogeneity in pancreatic cancer – Lou E

Discussion of abstract 4021

- Knowledge of the genetic driving signals regulating the growth of pancreatic cancer is currently limited and is a major barrier to formulating rational approaches to molecular targeting in pancreatic cancer
- Identifying cellular and molecular heterogeneity in pancreatic tumours with the use of new technologies such as next-generation sequencing could guide rational therapies and future clinical trials

Discussion of abstract 4023

- The study provides a shift in the paradigm of pancreatic cancers as being either KRAS wild-type or mutated: sub-clone populations exist with varying allelic ratios of KRAS
- Intratumoral heterogeneity of KRAS and tumour-stroma interactions play a larger role in tumour evasion and chemotherapy resistance than previously thought
- There was a wide range of allelic ratios of KRAS and cellular heterogeneity reported in 142 patients
  - Different concentrations of KRAS may dictate differences in tumour aggressiveness and patient survival

Outside of the proverbial box: Molecular and cellular heterogeneity in pancreatic cancer – Lou E

Discussion of abstract 4022

- Johansen et al., reported a significant improvement in OS with the combination of both low KRAS circulating tumour (ct) DNA and low serum CA19-9 in patients with unresected pancreatic cancer
- Considerations:
  - The sensitivity/specificity of ctDNA assays is yet to be determined
  - Is there an advantage of using isolated ctDNA compared with DNA from circulating tumour cells or enumerating circulating tumour cells as a prognostic marker?
  - Financial considerations
- NCI RAS Initiative is currently examining the role of mutations of Ras genes in 6 human tumour types
- The stroma is a very dynamic and proactive component of pancreatic carcinomas with intratumoral stroma varying significantly between patients
- Advances in molecular techniques and understanding of tumour biology can provide insight into the complex interplay of KRAS with tumour-stromal interactions