GI SLIDE DECK 2015

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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 the 2015 Gastrointestinal Cancers Symposium.

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
Phillippe Rougier
Thomas Seufferlein

(ESDO Governing Board Executives)

esdo

european society of digestive oncology

ESDO Medical Oncology Slide Deck
Editors 2015

COLORECTAL CANCERS



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Prof Wolff Schmiegel	Department of Medicine, Ruhr University, Bochum, Germany
Prof Thomas Gruenberger	Department of Surgery I, Rudolf Foundation Clinic, Vienna, Austria

PANCREATIC CANCER AND HEPATOBILIARY TUMOURS


Prof Jean-Luc Van Laetham	Department of Gastroenterology-GI Cancer Unit, Erasme University Hospital, Brussels, Belgium
Prof Thomas Seufferlein	Clinic of Internal Medicine I, University of Ulm, Ulm, Germany

GASTRO-OESOPHAGEAL AND NEUROENDOCRINE TUMOURS


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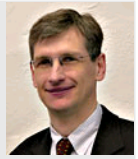
Prof Côme Lepage	University Hospital & INSERM, Dijon, France

BIOMARKERS

Prof Eric Van Cutsem	Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium
Prof Thomas Seufferlein	Clinic of Internal Medicine I, University of Ulm, Ulm, Germany

esdo

Glossary

5-FU	5-fluorouracil
ADC	adenocarcinoma
AE	adverse event
ALT	alanine transaminase
AST	aspartate aminotransferase
bid	twice daily
CCR2	chemokine receptor 2
CI	confidence interval
CT	chemotherapy
CR	complete response
CRC	colorectal cancer
CRT	chemoradiotherapy
DCR	disease control rate
DSS	disease specific survival
EHCCA	extrahepatic cholangiocarcinoma
eNOS	endothelial nitric oxide synthase
FGFR	fibroblast growth factor receptor
FOLFIRI	leucovorin, fluorouracil, irinotecan
FOLFIRINOX	leucovorin, fluorouracil, irinotecan, oxaliplatin
FOLFOX	oxaliplatin, fluorouracil, and leucovorin
GEC	gastroesophageal adenocarcinoma
GEJ	gastroesophageal junction
HCC	hepatocellular carcinoma
HMI	hybrid minimally invasive oesophagectomy
HR	hazard ratio
IHC	immunohistochemistry
IHCA	intrahepatic cholangiocarcinoma
iv	intravenous
KPS	Karnofsky Performance Status
LADG	laparoscopy assisted distal gastrectomy
LR	local recurrence
LV	leucovorin
mAb	monoclonal antibody
mCRC	metastatic colorectal cancer
MMC	mitomycin C
MTD	maximum tolerated dose
NOM	non-operative management
NSAID	nonsteroidal anti-inflammatory drugs
OC	oesophageal cancer
ODG	open distal gastrectomy
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PDGFR	platelet-derived growth factor receptor
PFS	progression free survival
PK	pharmacokinetic
PR	partial response
RECIST	Response Evaluation Criteria In Solid Tumors
RT	radiotherapy
SMA	superior mesenteric artery
TEAE	treatment emergent adverse event
TTP	time to progression
ULN	upper limit of normal
VEGFR	vascular endothelial growth factor receptor
QoL	quality of life
SCC	squamous cell carcinoma
SD	stable disease
SoC	standard of care

Contents

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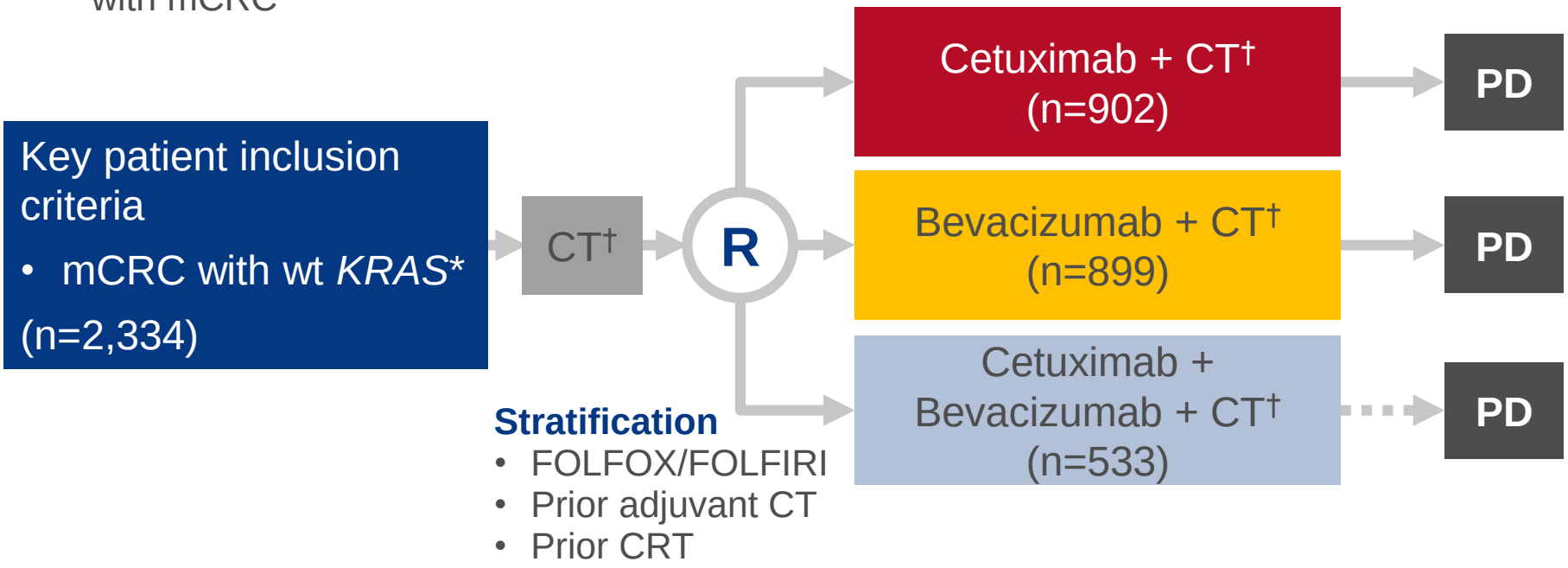
COLORECTAL CANCER

507: Vitamin D status and survival of metastatic colorectal cancer patients: Results from CALGB/SWOG 80405 (Alliance) – Ng K, et al

Study objective

- To determine if higher vitamin D levels are associated with improved survival in patients with mCRC



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINT

- PFS

- Plasma 25(OH)D levels were measured at baseline by radioimmunoassay
  - Vitamin D cohort: n=1,043; final trial cohort: n=1,137

*Original study design included unselected patients;
†FOLFIRI or FOLFOX (investigator choice)

Ng et al. J Clin Oncol 2015; 33 (suppl 3; abstr 507)

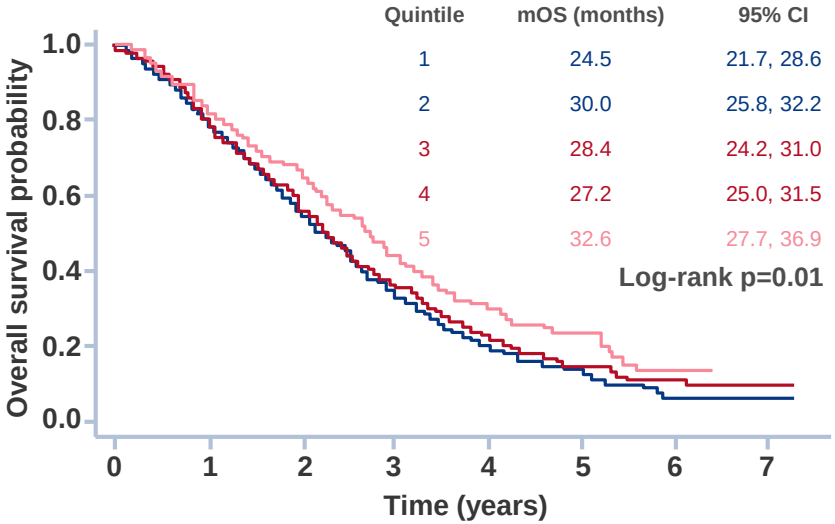
507: Vitamin D status and survival of metastatic colorectal cancer patients: Results from CALGB/SWOG 80405 (Alliance) – Ng K, et al

Key results

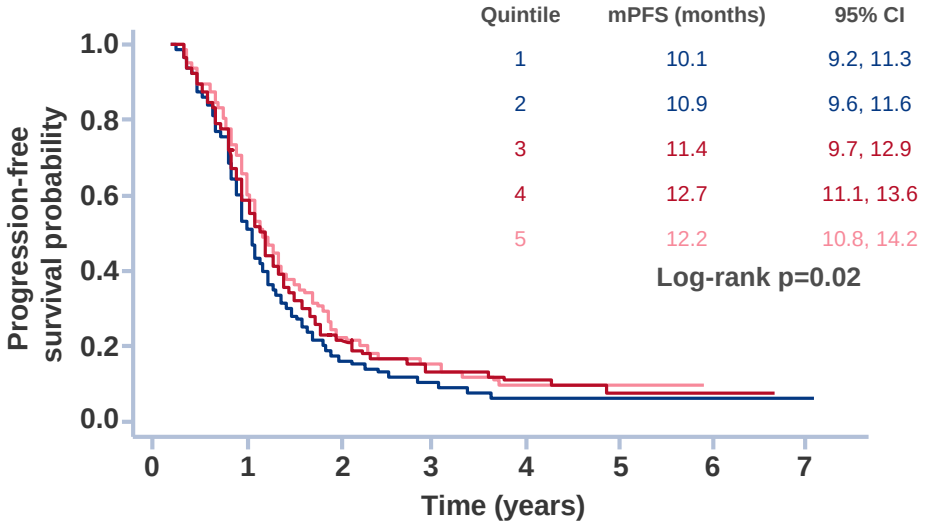
- Significantly lower baseline vitamin D levels were seen in patients living in the North/ Northeast (p<0.0001); obese patients (p=0.0006); less physically active patients (p=0.004)

	Quintile 1 (n=208)	Quintile 2 (n=209)	Quintile 3 (n=208)	Quintile 4 (n=210)	Quintile 5 (n=208)
Median 25(OH)D, ng/mL	8.0	13.6	17.2	21.4	27.5

OS according to baseline vitamin D level*



PFS according to baseline vitamin D level*



*Quintile number was proportional to baseline vitamin D level

Ng et al. J Clin Oncol 2015; 33 (suppl 3; abstr 507)

507: Vitamin D status and survival of metastatic colorectal cancer patients: Results from CALGB/SWOG 80405 (Alliance) – Ng K, et al

Key results (cont.)

- Multivariate analysis
  - Patients with the highest vitamin D levels (>24.1 ng/mL) had the greatest improvement in OS (HR 0.65; 95% CI 0.51, 0.83) and PFS (HR 0.79; 95% CI 0.63, 0.99)
- The improvement in OS was maintained across subgroups of patient characteristics, including *KRAS* status

Conclusions

- **Patients with mCRC are frequently vitamin D deficient**
- **Higher vitamin D levels were associated with significantly improved OS and PFS**
- **A Phase II randomised trial is currently underway to investigate the impact of vitamin D supplementation in combination with chemotherapy**

Ng et al. J Clin Oncol 2015; 33 (suppl 3; abstr 507)

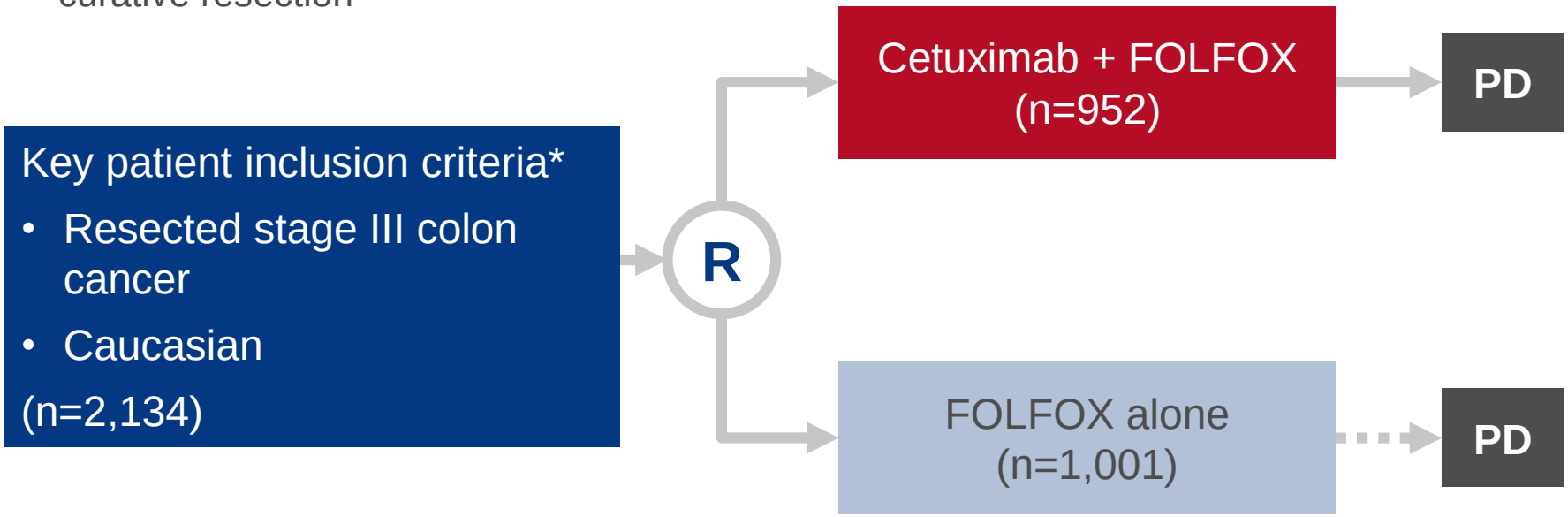
COLORECTAL CANCER

COLON CANCER

508: HapB3 and the deep intronic variant c.1129-5923 C>G of the dihydropyrimidine dehydrogenase gene (DPYD) to predict toxicity in stage III colon cancer (CC) patients (pts) (NCCTG Alliance N0147) – Lee AM, et al

Study objective

- *Post hoc* analysis of the NCCTG N0147 trial to assess the relationship between the *DPYD* HapB3 haplotype, the deep intronic variant and severe AEs commonly related to 5-FU-based therapy (grade 3+) in stage III colon cancer receiving adjuvant CT after curative resection



- *DPYD* variants were genotyped and the proportion of patients with ≥1 grade 3+ AEs was determined

*Patients with the functionally deleterious *DPYD* variants *DPYD*2A*, D949V, and I560S were excluded from the primary cohort

Lee et al. J Clin Oncol 2015; 33 (suppl 3; abstr 508)

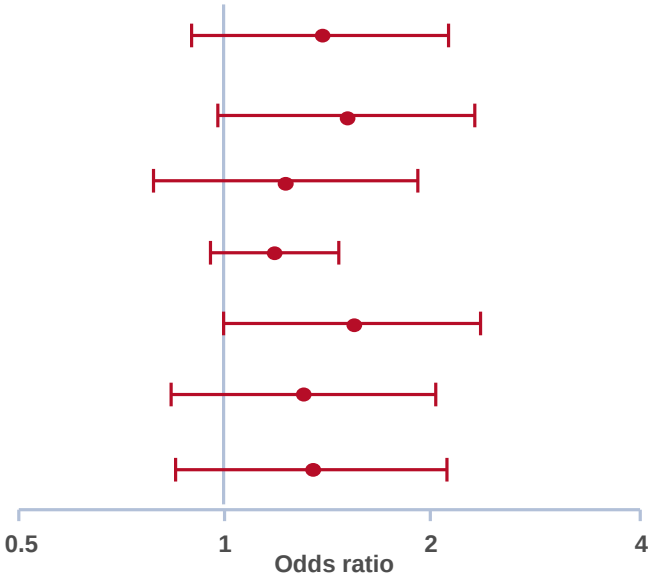
508: HapB3 and the deep intronic variant c.1129-5923 C>G of the dihydropyrimidine dehydrogenase gene (DPYD) to predict toxicity in stage III colon cancer (CC) patients (pts) (NCCTG Alliance N0147) – Lee AM, et al

Key results

- Grade 3+ overall AEs and 5-FU-related AEs were reported in 1,339 patients (62.8%) and 705 patients (33.0%), respectively

Univariate association with 5-FU-related Grade 3+ AEs (n=2,134)

DPYD Variant	Carrier AE/Total (%)	Wild-type AE/Total (%)	Odds ratio (95% CI)	P-value
rs115349832 c.959–51 T>C	38/95 (40.0)	667/2039 (32.7)	1.371 (0.900, 2.089)	0.1413
rs56038477 c.1236 G>A, E412E	38/90 (42.2)	667/2044 (32.6)	1.509 (0.983, 2.316)	0.599
rs56276561 c.483+18 G>A	33/88 (37.5)	672/2046 (32.8)	1.227 (0.789, 1.907)	0.3640
rs6668296 c.680+139 G>A	165/457 (36.1)	540/1677 (32.2)	1.190 (0.958, 1.478)	0.1159
rs75017182 c.1129–5923 C>G	38/89 (42.7)	667/2045 (32.6)	1.539 (1.001, 2.367)	0.0493
HapB3	33/85 (38.8)	672/2049 (32.8)	1.300 (0.833, 2.031)	0.2482
HapB3 rs75017182	33/84 (39.3)	672/2050 (32.8)	1.327 (0.848, 2.076)	0.2154



Conclusions

- **Grade 3+ 5-FU-related AEs were significantly associated with *DPYD* HapB3 variants and the deep intronic c.1129-5923 C>G variant**
- **These variants (in the absence of DPYD*2A, D949V and I560S) predicted toxicity to adjuvant 5-FU-based CT in Caucasian patients with stage III colon cancer**

Lee et al. J Clin Oncol 2015; 33 (suppl 3; abstr 508)

COLORECTAL CANCER

RECTAL CANCER

509: Organ preservation in patients with rectal cancer with clinical complete response after neoadjuvant therapy – Smith JJ, et al

Study objective

- To assess the safety and efficacy of non-operative management (NOM) in patients with rectal cancer (Stages I–III) following complete response (CR) to neoadjuvant therapy

Study design

- Retrospective review comparing NOM versus rectal resection (n=442)
- Patients either achieved clinical CR and were treated with NOM, or underwent rectal resection and achieved a pathologic CR
  - Rectal resection: CRT (5040 cGy + 5-FU), then surgery, then adjuvant CT
  - NOM: Adjuvant CT, then neoadjuvant FOLFOX, then CRT (as above), then surgery
- Kaplan-Meier estimates and the log-rank test were used; median follow-up was 3.5 years

Smith et al. J Clin Oncol 2015; 33 (suppl 3; abstr 509)

509: Organ preservation in patients with rectal cancer with clinical complete response after neoadjuvant therapy – Smith JJ, et al

Key results

	N	Local regrowth, n (%)	LR after resection, n	DSS, n (%)	OS, n (%)	Rectal preservation, n (%)
NOM	73	19 (26)	1	69 (91)	67 (91)	56* (72)
Resection	72	0	0	70 (96)	68 (95)	0

- Most local re-growths occurred within 12–13 months and could be salvaged by surgery
  - Pelvic recurrence after surgical salvage: n=1 (1.5%)

	NOM, %	Resection, %
1-year distance recurrence rate	7.2	1.5
4-year distance recurrence rate	17.3	8.6

Conclusions

- **NOM appeared to be a safe and effective treatment in patients with rectal cancer**
- **NOM had a high rate of rectal preservation and a similar rate of OS/DSS as resection**
- **Prospective trials are currently in progress to confirm these findings**

*Includes two patients with local regrowth requiring local excision only.
DSS, disease specific survival; LR, local recurrence

Smith et al. J Clin Oncol 2015; 33 (suppl 3; abstr 509)

510: Optimal timing of surgical resection after radiation therapy in locally advanced rectal adenocarcinoma: An analysis of the National Cancer Database (NCDB) – Huntington CR, et al

Study objective

- To determine the optimal interval between the end of radiation therapy and surgical resection in locally advanced rectal adenocarcinoma using the National Cancer Database (NCDB)

Study design

- Patients with adenocarcinoma of the rectum and no evidence of metastasis at diagnosis, who underwent pre-operative chemoradiation followed by radical surgical resection from the NCDB were identified (N=6,805)

Primary endpoints

- Survival after time of diagnosis
- Rate of positive surgical margin
- Rate of complete pathological response

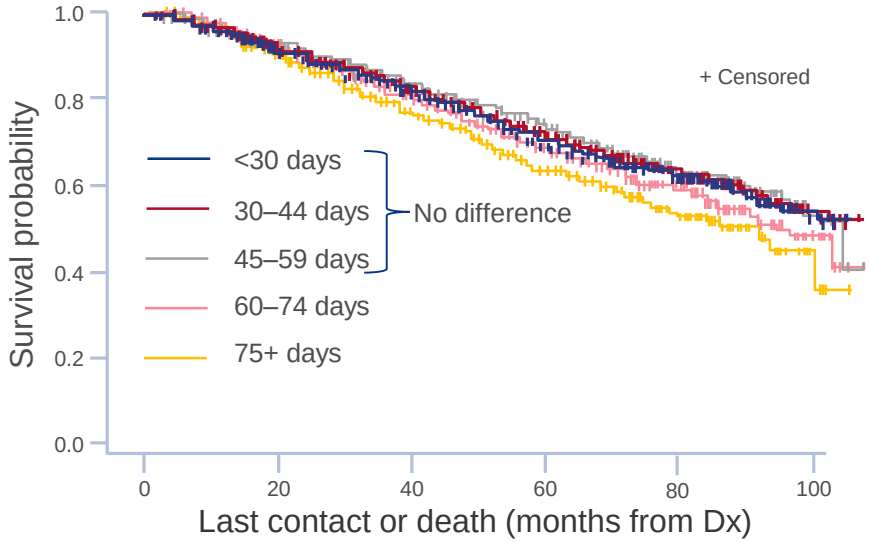
Huntington et al. J Clin Oncol 2015; 33 (suppl 3; abstr 510)

510: Optimal timing of surgical resection after radiation therapy in locally advanced rectal adenocarcinoma: An analysis of the National Cancer Database (NCDB) – Huntington CR, et al

Key results

- OS was shorter for R-S interval >60 days vs. <60 days (HR 1.25)
  - OS was equivalent in groups with R-S interval <60 days
- Increasing R-S interval was associated with an increase in:
  - the rate of pCR up to 75 days after radiation and did not increase further thereafter (p=0.0003 Chi-squared)
  - positive surgical margin rate beyond 60 days of radiation (p=0.0067 Chi-squared); positive surgical margins occurred at equivalent rates in groups of R-S interval <60 days

R-S interval, days	n (%)	pCR, %
<30	517 (7.6)	3.7
31–45	2,325 (34)	5.7
46–60	2,505 (37)	7.7
61–75	926 (14)	8.8
75+	532 (7.0)	7.0
p=0.0003 Chi-squared		



Conclusion

- **A delay of >60 days from radiation to surgical resection and subsequent chemotherapy is associated with a decrease in OS in patients with rectal cancer**

R-S, radiation-surgery

Huntington et al. J Clin Oncol 2015; 33 (suppl 3; abstr 510)

COLORECTAL CANCER

LIVER METASTASES

511: Effect of preoperative hepatic and regional arterial chemotherapy on metachronous liver metastasis after curative colorectal cancer resection: A prospective, multicenter, randomized controlled trial – Xu J, et al

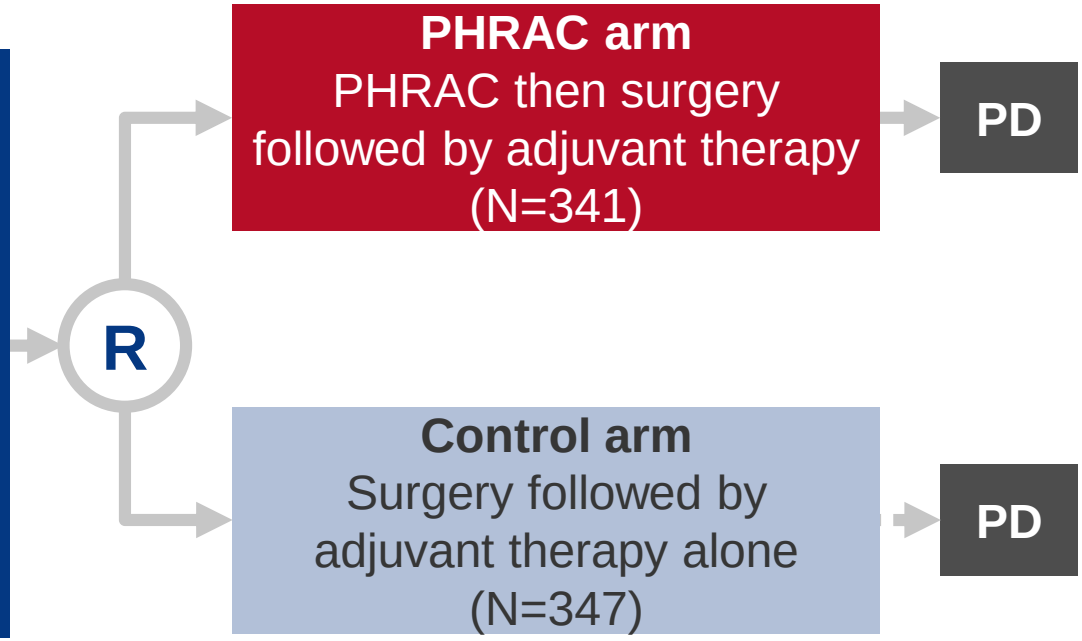
Study objective

- To evaluate the addition of PHRAC* prior to surgery and adjuvant therapy (mFOLFOX6) in patients with Stage II and III colorectal cancer

Key patient inclusion criteria

- Age 18–75 years
- cTNM Stage II/III
- No distant metastases
- No contraindications to chemotherapy
- No previous cancer therapy

(N=688)



PRIMARY ENDPOINT

- DFS

SECONDARY ENDPOINTS

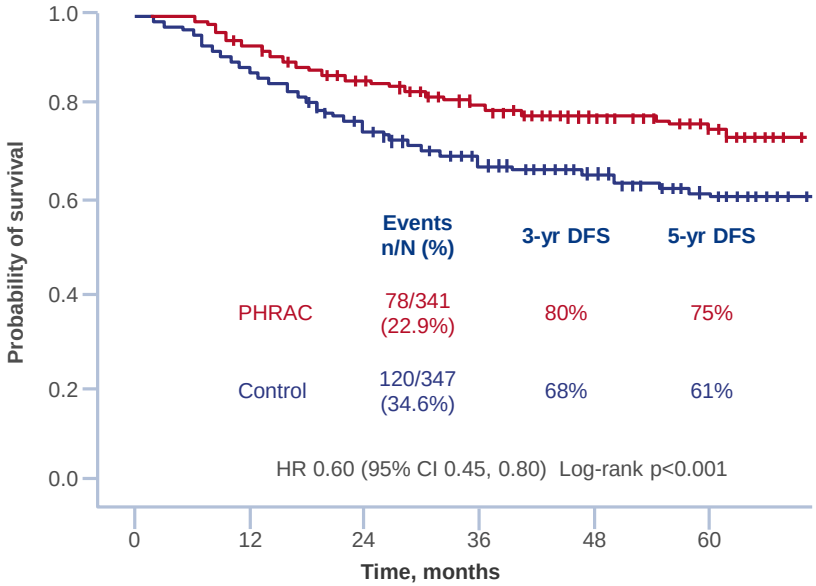
- Cumulative incidence of metachronous liver metastasis, OS, safety

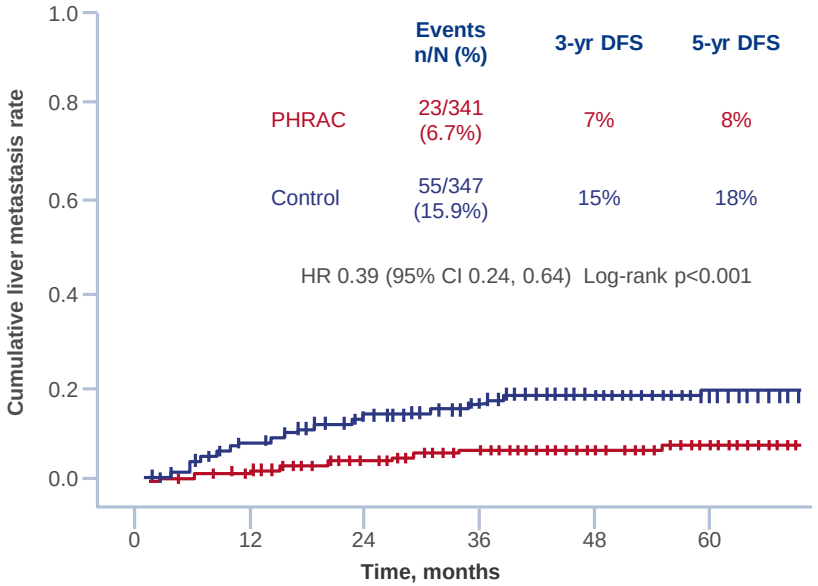
*5-FU 650 mg/m^2, oxaliplatin 75 mg/m^2, MMC 8 mg/m^2: half in each artery (superior mesenteric artery and hepatic artery).
PHRAC, preoperative hepatic and regional arterial CT

Xu et al. J Clin Oncol 2015; 33 (suppl 3; abstr 511)

511: Effect of preoperative hepatic and regional arterial chemotherapy on metachronous liver metastasis after curative colorectal cancer resection: A prospective, multicenter, randomized controlled trial – Xu J, et al

Key results





- Five-year OS was 81% and 72% in PHRAC and control arms, respectively (HR 0.59; 95% CI 0.42, 0.84 [p=0.003])
- No significant differences in morbidity or mortality were noted between the two arms
- Subgroup analysis showed that the differences in DFS, liver metastasis rate and OS were significant between the two arms in stage III patients, but not in stage II patients

Conclusion

- **Addition of PHRAC can improve DFS and OS and reduces the incidence of liver metastasis in patients with Stage III colorectal cancer**

Xu et al. J Clin Oncol 2015; 33 (suppl 3; abstr 511)

COLORECTAL CANCER

SECOND AND FURTHER LINES OF TREATMENT

512: RAISE: A randomized, double-blind, multicenter phase III study of irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) plus ramucirumab (RAM) or placebo (PBO) in patients (pts) with metastatic colorectal carcinoma (CRC) progressive during or following first-line combination therapy with bevacizumab (bev), oxaliplatin (ox), and a fluoropyrimidine (fp) – Tabernero J, et al

Study objective

- To assess the efficacy and safety of second-line ramucirumab plus FOLFIRI following first-line therapy with bevacizumab, oxaliplatin and a fluoropyrimidine in patients with mCRC

Key patient inclusion criteria

- mCRC
- ECOG PS 0–1
- Known *KRAS* status
- PD after first-line bevacizumab (≥2 doses) + oxaliplatin + fluoropyrimidine
- Progression ≤6 months after last dose of first-line therapy

(n=1,072)

R 1:1

Ramucirumab (8 mg/kg) + FOLFIRI* q2w (n=536) → PD

Placebo + FOLFIRI* q2w (n=536) → PD

Stratification

- Geographic regions
- *KRAS* status
- Time to PD after first-line therapy

PRIMARY ENDPOINT(S)

- OS

SECONDARY ENDPOINTS

- PFS, ORR, safety

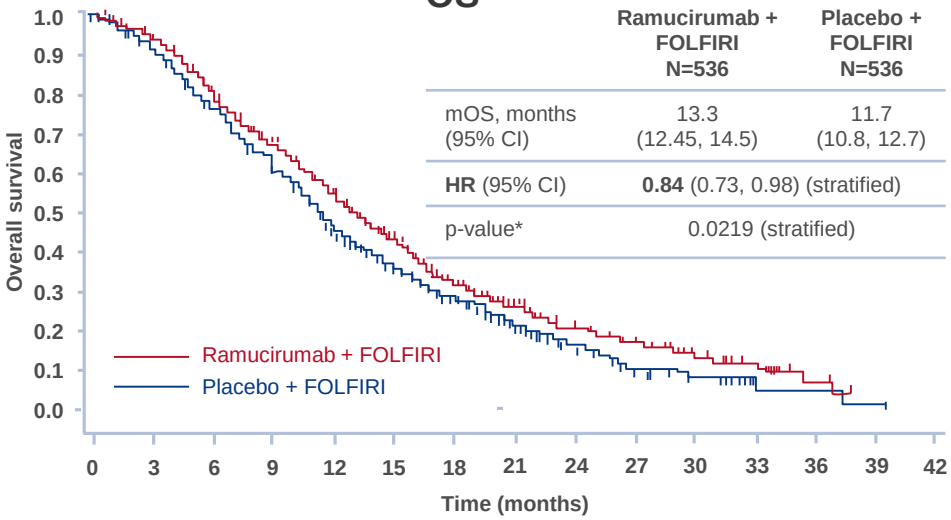
*Irinotecan 180 mg/m^2, folinic acid 400 mg/m^2, 5-fluorouracil 400 mg/m^2 bolus then 2,400 mg/m^2 continuous iv over 46–48 hrs

Tabernero et al. J Clin Oncol 2015; 33 (suppl 3; abstr 512)

512: RAISE: A randomized, double-blind, multicenter phase III study of irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) plus ramucirumab (RAM) or placebo (PBO) in patients (pts) with metastatic colorectal carcinoma (CRC) progressive during or following first-line combination therapy with bevacizumab (bev), oxaliplatin (ox), and a fluoropyrimidine (fp) – Tabernero J, et al

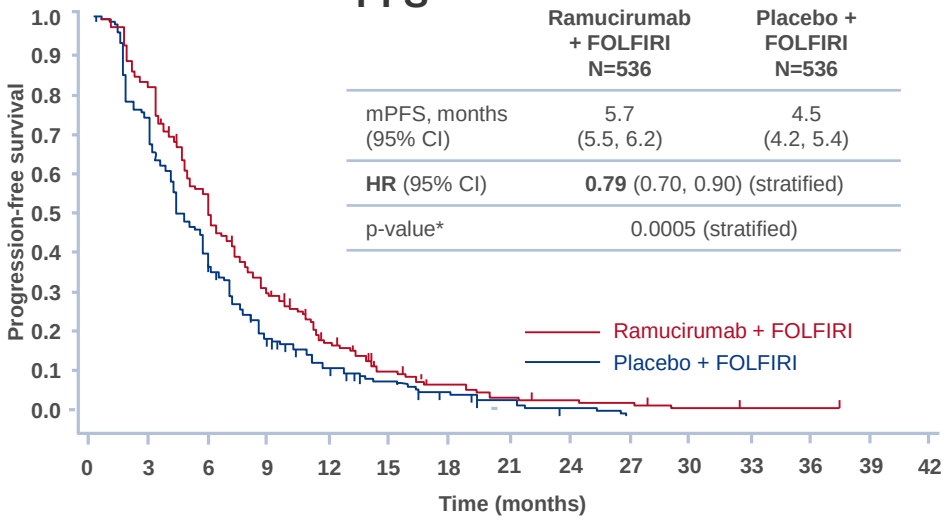
Key results

OS



	Ramucirumab + FOLFIRI N=536	Placebo + FOLFIRI N=536
mOS, months (95% CI)	13.3 (12.45, 14.5)	11.7 (10.8, 12.7)
HR (95% CI)	**0.84** (0.73, 0.98) (stratified)	
p-value*	0.0219 (stratified)	

PFS



	Ramucirumab + FOLFIRI N=536	Placebo + FOLFIRI N=536
mPFS, months (95% CI)	5.7 (5.5, 6.2)	4.5 (4.2, 5.4)
HR (95% CI)	**0.79** (0.70, 0.90) (stratified)	
p-value*	0.0005 (stratified)	

Tumour response, %	Ramucirumab + FOLFIRI (N=536)	Placebo + FOLFIRI (N=536)	p-value
Response rate (CR + PR)	13.4	12.5	0.6336
Disease control rate (CR + PR + SD)	74.1	68.8	0.0587
CR	0	0.4	
PR	13.4	12.1	
SD	60.6	56.3	
PD	16.2	25.0	

*Log-rank

Tabernero et al. J Clin Oncol 2015; 33 (suppl 3; abstr 512)

512: RAISE: A randomized, double-blind, multicenter phase III study of irinotecan, folinic acid, and 5-fluorouracil (FOLFIRI) plus ramucirumab (RAM) or placebo (PBO) in patients (pts) with metastatic colorectal carcinoma (CRC) progressive during or following first-line combination therapy with bevacizumab (bev), oxaliplatin (ox), and a fluoropyrimidine (fp) – Tabernero J, et al

Key results (cont.)

- Mean overall relative dose intensity: ramucirumab 81.79% vs. placebo 87.97%

AEs, %	Any grade		Grade ≥3	
	Ramucirumab + FOLFIRI (n=529)	Placebo + FOLFIRI (n=528)	Ramucirumab + FOLFIRI (n=529)	Placebo + FOLFIRI (n=528)
Any TEAE (≥50% any grades)	98.7	98.3	79.0	62.3
Neutropenia	58.8	45.6	38.4	23.3
Fatigue	57.7	52.1	11.5	7.8
Diarrhoea	59.7	51.3	10.8	9.7
Nausea	49.5	51.3	2.5	2.7
AEs of special interest (≥15% any grades)				
Bleeding/haemorrhage	43.9	22.7	2.5	1.7
Hypertension	26.1	8.5	11.2	2.8
Proteinuria	17.0	4.5	3.0	0.2

Conclusions

- **RAISE met its primary endpoint**
  - **Ramucirumab + FOLFIRI significantly improved OS vs. placebo + FOLFIRI as second-line therapy in patients with mCRC**
- **Ramucirumab + FOLFIRI was well tolerated and AEs were considered manageable**

Tabernero et al. J Clin Oncol 2015; 33 (suppl 3; abstr 512)

513: A randomized, double-blind, parallel-group, placebo-controlled, multicenter, phase II clinical study of famitinib in the treatment of advanced metastatic colorectal cancer – Xu RH, et al

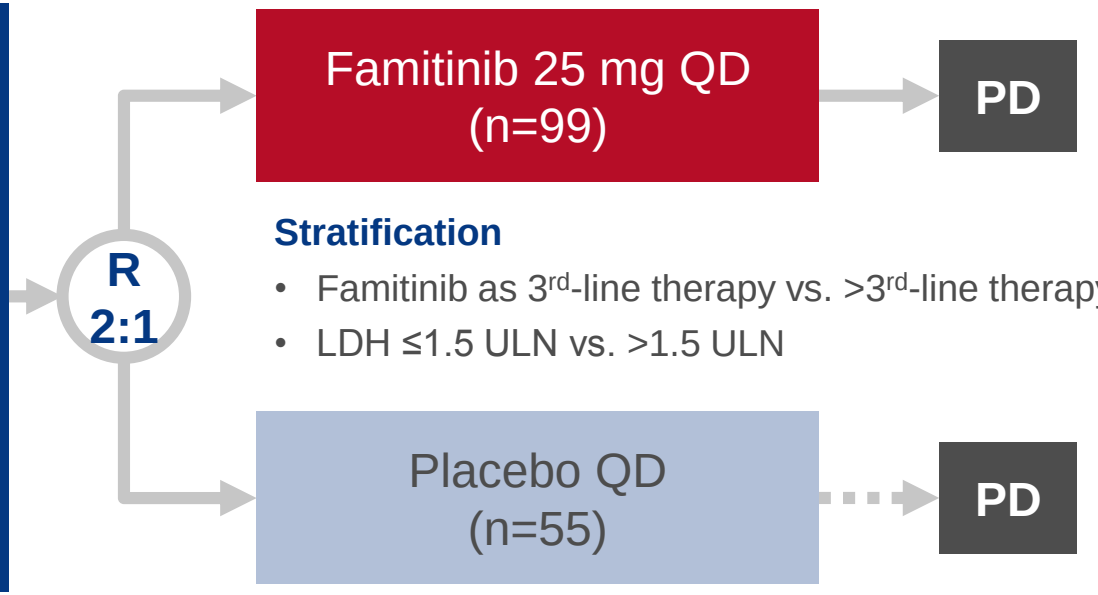
Study objective

- To assess the efficacy and safety of famitinib, a multi-targeted tyrosine kinase inhibitor*, in the treatment of advanced CRC

Key patient inclusion criteria

- ECOG PS 0–1
- Age 18–70 years
- Recurrent/metastatic CRC
- Failed ≥2 standard CT†
- ≥1 measurable legion according to RECIST 1.1

(n=167)



PRIMARY ENDPOINT(S)

- PFS

SECONDARY ENDPOINTS

- OS, ORR, DCR, QoL

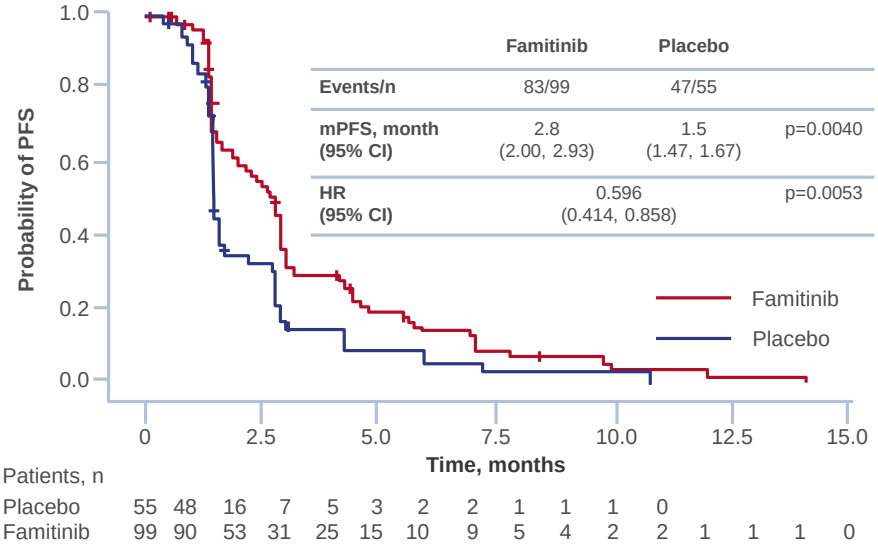
*Primarily targets VEGFR2, c-Kit and PDGFR;
†Including 5-FU, irinotecan, oxaliplatin

Xu et al. J Clin Oncol 2015; 33 (suppl 3; abstr 513)

513: A randomized, double-blind, parallel-group, placebo-controlled, multicenter, phase II clinical study of famitinib in the treatment of advanced metastatic colorectal cancer – Xu RH, et al

Key results

PFS



Patients, n

Placebo	55	48	16	7	5	3	2	2	1	1	1	0			
Famitinib	99	90	53	31	25	15	10	9	5	4	2	2	1	1	1	0

	Famitinib (n=99)	Placebo (n=55)	p-value
mOS, months	7.5	7.6	0.604
HR (95% CI)	1.10 (0.76, 1.60)		0.605
ORR, %	2.2	0.0	0.54
DCR, %	59.8	31.4	0.0016

- Grade 3/4 AEs (occurring in ≥10% in either group) for famitinib vs. placebo were: hypertension 11.1% vs. 1.8%; thrombocytopenia 10.1 vs. 1.8%; hand-foot syndrome 10.1% vs. 0.0%; and increased γ-GT 7.1% vs. 12.7%

Conclusions

- **Famitinib monotherapy improved PFS in patients with advanced/metastatic CRC**
- **mOS was not significantly different between famitinib and placebo**
- **Famitinib demonstrated a similar safety profile to other VEGFR agents**

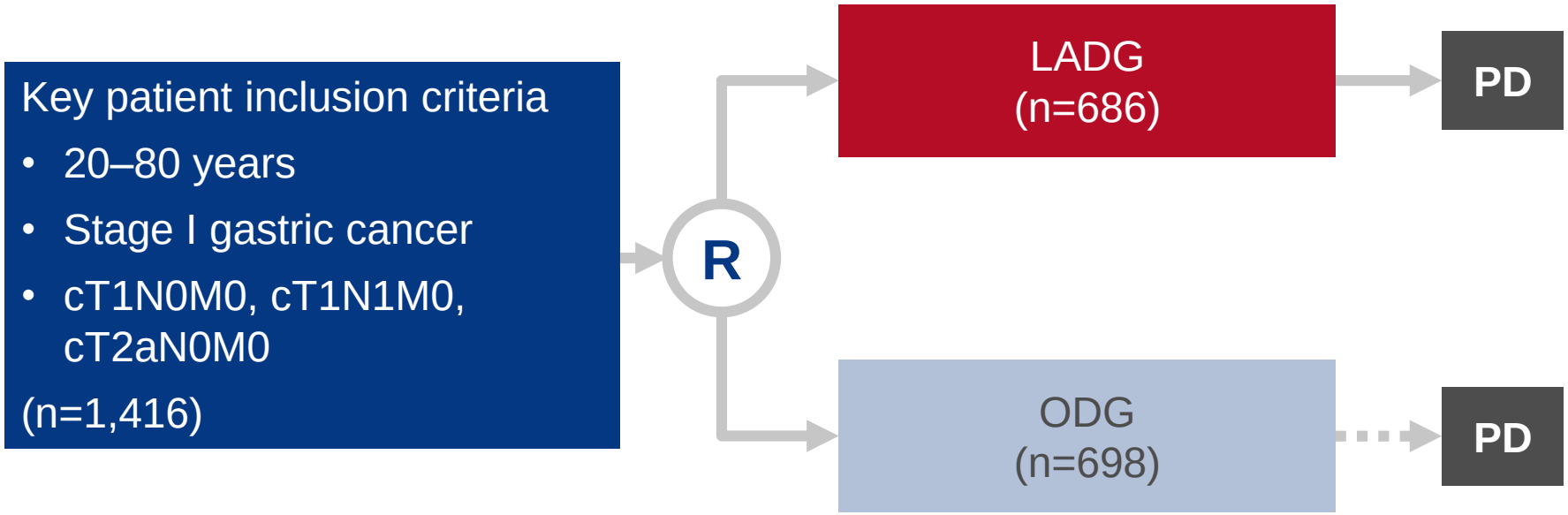
Xu et al. J Clin Oncol 2015; 33 (suppl 3; abstr 513)

OESOPHAGEAL AND GASTRIC CANCER

4: Morbidity and mortality after laparoscopy-assisted and open distal gastrectomy for stage I gastric cancer: Results from a multicenter randomized controlled trial (KLASS-01) – Hyuk-Joon L, et al

Study objective

- To compare the safety of laparoscopy-assisted versus open distal gastrectomy in patients with Stage I gastric cancer



PRIMARY ENDPOINT

- Non-inferior 5-year OS

SECONDARY ENDPOINTS

- Morbidity and mortality, 5-year DFS
- QoL, cost-effectiveness

LADG, laparoscopy assisted distal gastrectomy;
ODG, open distal gastrectomy

Hyuk-Joon et al. J Clin Oncol 2015; 33 (suppl 3; abstr 4)

4: Morbidity and mortality after laparoscopy-assisted and open distal gastrectomy for stage I gastric cancer: Results from a multicenter randomized controlled trial (KLASS-01) – Hyuk-Joon L, et al

Key results

Morbidity and mortality, n (%)	LADG (N=644)	ODG (N=612)	p-value
Postoperative morbidity	**84 (13.0)**	**122 (19.9)**	**0.001**
Intra-abdominal complications	49 (7.6)	63 (10.3)	0.095
Wound complications	**20 (3.1)**	**47 (7.7)**	**<0.001**
Medical complications	19 (3.0)	18 (2.9)	0.992
Surgical mortality	4 (0.6)	2 (0.3)	0.687
Re-operation	8 (1.2)	9 (1.5)	0.726

Risk factors for postoperative mortality*	OR (95% CI)	p-value
LADG vs. ODG	**0.599 (0.441, 0.813)**	**0.001**
No. of comorbidities		
1 vs. 0	1.307 (0.927, 1.843)	0.126
2 vs. 0	1.578 (0.970, 2.588)	0.066
3 vs. 0	**3.602 (1.508, 8.662)**	**0.004**

*Multivariate analysis

Hyuk-Joon et al. J Clin Oncol 2015; 33 (suppl 3; abstr 4)

4: Morbidity and mortality after laparoscopy-assisted and open distal gastrectomy for stage I gastric cancer: Results from a multicenter randomized controlled trial (KLASS-01) – Hyuk-Joon L, et al

Conclusion

- **LADG for patients with clinical Stage I gastric cancer is safe and is associated with a lower occurrence of wound complications than standard ODG**

Hyuk-Joon et al. J Clin Oncol 2015; 33 (suppl 3; abstr 4)

5: Hybrid minimally invasive versus open oesophagectomy for patients with oesophageal cancer: A multicenter, open-label, randomized phase III controlled trial, the MIRO trial – Mariette C, et al

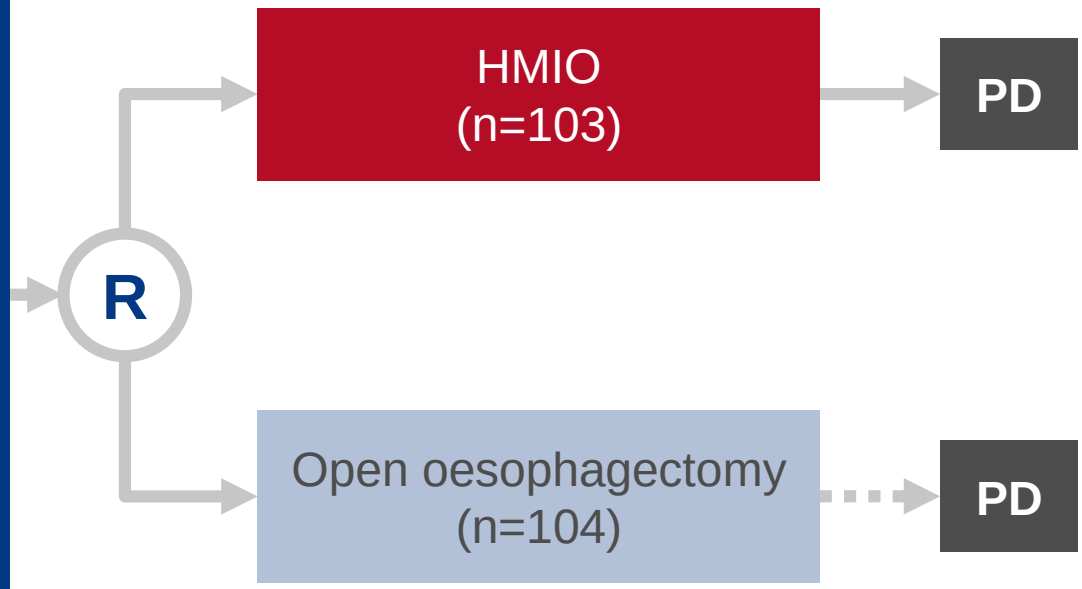
Study objective

- To assess the postoperative morbidity and mortality of HMIO versus open transthoracic oesophagectomy in patients with oesophageal cancer

Key patient inclusion criteria

- Resectable SCC or ADC
- Infracarinal OC with Ivor Lewis procedure scheduled
- Primary surgery or neoadjuvant therapy
- Age >18–<75 years
- WHO PS 0–2

(n=212)



PRIMARY ENDPOINT

- Postoperative morbidity

SECONDARY ENDPOINTS

- Postoperative mortality, DFS, OS
- Major pulmonary complication
- QoL, medico-economic analysis

HMIO, hybrid minimally invasive oesophagectomy

Mariette et al. J Clin Oncol 2015; 33 (suppl 3; abstr 5)

5: Hybrid minimally invasive versus open oesophagectomy for patients with oesophageal cancer: A multicenter, open-label, randomized phase III controlled trial, the MIRO trial – Mariette C, et al

Key results

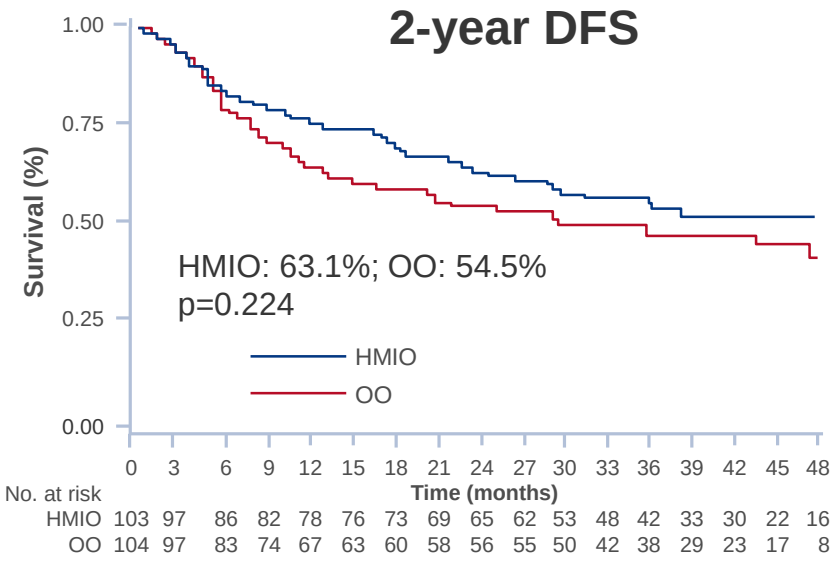
	HMIO (n=103)	OO (n=104)
Postoperative morbidity Grade II–IV, n (%)	**37 (35.9)**	**67 (64.4)**
OR (95% CI); p-value	**0.31 (0.18, 0.55); <0.0001**	
Mortality, n (%)	1 (1.0)	2 (1.9)
Medical mortality, n (%)	20 (19.6)	41 (39.8)
Major pulmonary complication, n (%)	**18 (17.7)**	**31 (30.1)**
p-value	**0.037**	
Surgical mortality, n (%)	15 (14.7)	21 (20.4)
Anastomotic leakage, n (%)	8 (7.8)	5 (4.9)
Plastic necrosis, n (%)	2 (2.0)	3 (2.9)
Median LOS, days (range)	14 (7, 95)	14 (3, 218)

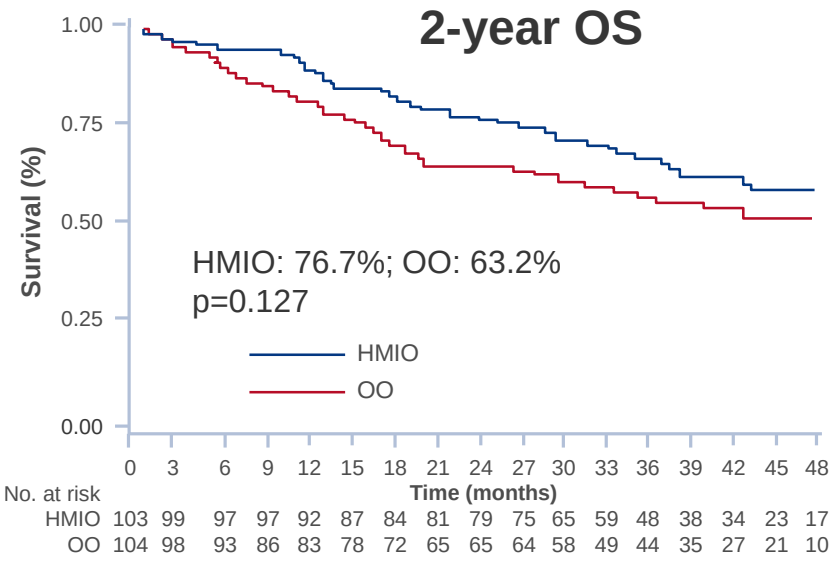
OO, open oesophagectomy

Mariette et al. J Clin Oncol 2015; 33 (suppl 3; abstr 5)

5: Hybrid minimally invasive versus open oesophagectomy for patients with oesophageal cancer: A multicenter, open-label, randomized phase III controlled trial, the MIRO trial – Mariette C, et al

Key results (cont.)





Conclusions

- HMIO provides reductions in severe and major pulmonary complications without negatively impacting on recurrence or survival
- These findings support the use of HMIO in patients with resectable oesophageal cancer
- HMIO should be considered as a new standard of care

Mariette et al. J Clin Oncol 2015; 33 (suppl 3; abstr 5)

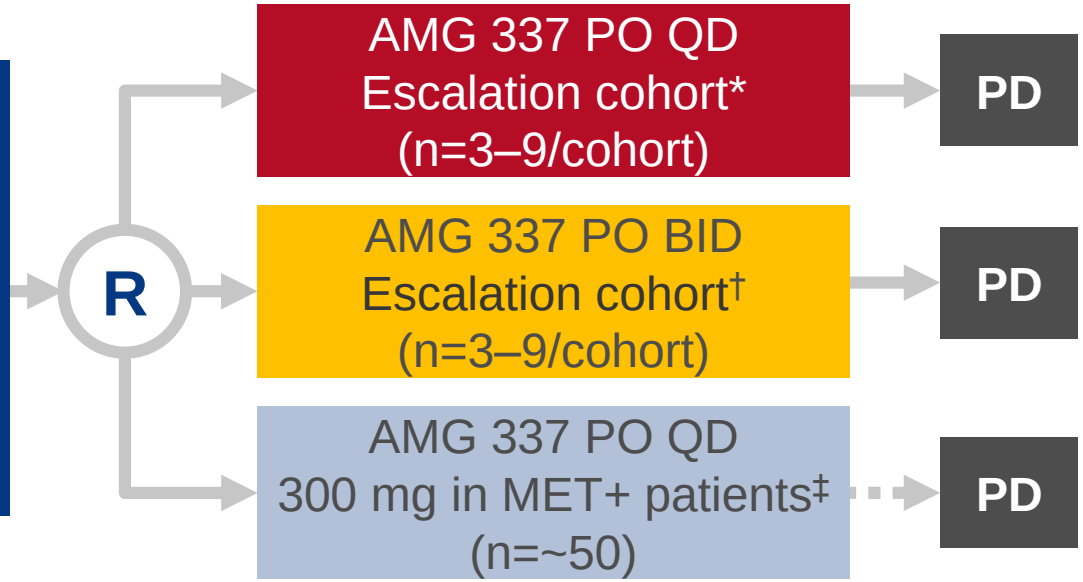
1: Clinical activity of AMG 337, an oral MET kinase inhibitor, in adult patients (pts) with MET-amplified gastroesophageal junction (GEJ), gastric (G), or esophageal (E) cancer – Kwak EL, et al

Study objective

- Phase I open-label study assessing the efficacy and safety of AMG 337, a highly selective small-molecule MET kinase inhibitor, in patients with GEJ, gastric or oesophageal cancer

Key patient inclusion criteria
- Advanced solid tumours
- ≥18 years
- ECOG PS ≤2
- Adequate organ function

(n=90)



PRIMARY ENDPOINTS

- Safety/tolerability, PK, MTD

SECONDARY ENDPOINTS

- Response by RECIST 1.1
- Correlation of *MET* status with response

*25, 50, 100, 150, 200, 300 or 400 mg; †100, 150, 200 or 250 mg; ‡Planned expansion cohort

Kwak et al. J Clin Oncol 2015; 33 (suppl 3; abstr 1)

1: Clinical activity of AMG 337, an oral MET kinase inhibitor, in adult patients (pts) with MET-amplified gastroesophageal junction (GEJ), gastric (G), or esophageal (E) cancer – Kwak EL, et al

Key results

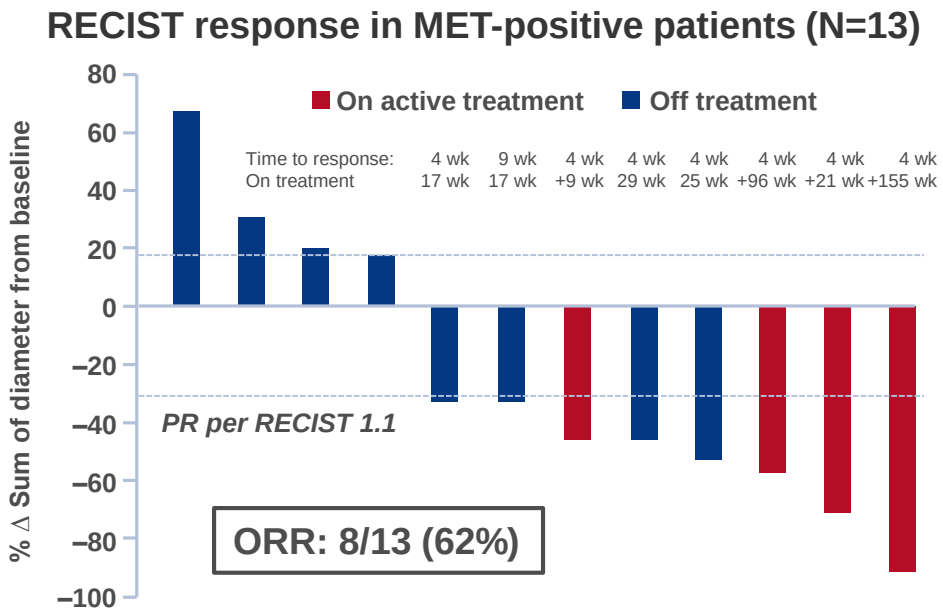
- *MET* amplification was present in 21% of patients
- Primary diagnosis: GEJ/gastric/oesophageal (23%), CRC (20%), sarcoma (11%), NSCLC (6%), melanoma (4%), CUP (3%), ovarian (3%), other (30%)

AEs occurring in ≥7%, n (%)	Grade 1 or 2	Grade ≥3
All AEs	56 (62.2)	19 (21.1)
Headache	47 (52.2)	7 (7.8)
Nausea	30 (33.3)	0
Vomiting	16 (17.8)	0
Dry skin	11 (12.2)	3 (3.3)
Peripheral oedema	11 (12.2)	1 (1.1)
Hypoalbuminaemia	10 (11.1)	0
Myalgia	8 (8.9)	0

Kwak et al. J Clin Oncol 2015; 33 (suppl 3; abstr 1)

1: Clinical activity of AMG 337, an oral MET kinase inhibitor, in adult patients (pts) with MET-amplified gastroesophageal junction (GEJ), gastric (G), or esophageal (E) cancer – Kwak EL, et al

Key results (cont.)



Conclusions

- AMG 337 demonstrated substantial response in patients with MET-amplified GEJ, gastric or oesophageal cancer
- The recommended Phase II dose of AMG 337 is 300 mg PO daily
- A Phase II study of AMG 337 in patients with MET-amplified GEJ, gastric or oesophageal cancer is currently recruiting patients (NCT02016534)

Kwak et al. J Clin Oncol 2015; 33 (suppl 3; abstr 1)

2: Randomized phase II study of FOLFOX +/- MET inhibitor, onartuzumab (O), in advanced gastroesophageal adenocarcinoma (GEC) – Shah MA, et al

Study objective

- To investigate the efficacy and safety of onartuzumab (MetMab) plus mFOLFOX6 in the first-line treatment of metastatic, HER2-negative gastroesophageal adenocarcinoma

Key patient inclusion criteria

- Gastroesophageal adenocarcinoma
- No prior therapy for metastatic disease
- Age >18 years
- ECOG PS 0–1
- HER2-negative

(n=123)

R 1:1

Onartuzumab 10 mg/kg + mFOLFOX6* q2w (n=62) → Onartuzumab → PD

Stratification

- Lauren histologic subtype
- Prior gastrectomy

Placebo + mFOLFOX6* q2w (n=61) → Placebo → PD

PRIMARY ENDPOINT

- PFS (ITT and †MET-positive population)

SECONDARY ENDPOINTS

- OS (ITT and †MET-positive population), ORR, safety

*Oxaliplatin 85 mg/m^2 + leucovorin 200 mg/m^2 + 5-fluorouracil 400 mg/m^2 bolus and 2400 mg/m^2 iv; †≥50% high staining by IHC

Shah et al. J Clin Oncol 2015; 33 (suppl 3; abstr 2)

2: Randomized phase II study of FOLFOX +/- MET inhibitor, onartuzumab (O), in advanced gastroesophageal adenocarcinoma (GEC) – Shah MA, et al

Key results

	ITT population		MET-positive subgroup	
	Onartuzumab (N=62)	Placebo (N=61)	Onartuzumab (N=16)	Placebo (N=19)
mPFS, months	**6.77**	**6.97**	**5.95**	**6.8**
HR (95% CI)	**1.06 (0.71, 1.63)**		**1.38 (0.60, 3.20)**	
p-value	0.7149		0.4514	
OS, months	10.61	11.27	8.51	8.48
HR (95% CI)	1.06 (0.64, 1.75)		1.12 (0.45, 2.78)	
p-value	0.8341		0.8021	
ORR, %	60.5	57.1		

- Asian patients had longer PFS and OS than non-Asian patients in both groups

Shah et al. J Clin Oncol 2015; 33 (suppl 3; abstr 2)

2: Randomized phase II study of FOLFOX +/- MET inhibitor, onartuzumab (O), in advanced gastroesophageal adenocarcinoma (GEC) – Shah MA, et al

Key results (cont.)

AEs (≥25%, any grade), %	Onartuzumab (N=60)	Placebo (N=60)
Nausea	68	63
Vomiting	47	45
Diarrhoea	48	40
Constipation	28	38
Abdominal pain	25	23
Peripheral neuropathy	37	42
Neutropenia	63	50
Fatigue	43	55
Peripheral oedema	55	15

Conclusions

- **Onartuzumab added to mFOLFOX6 did not improve PFS in patients with HER2-negative gastroesophageal adenocarcinoma, regardless of MET status**
- **The safety profile of onartuzumab was similar to previous studies**

Shah et al. J Clin Oncol 2015; 33 (suppl 3; abstr 2)

3: Relationship between PD-L1 expression and clinical outcomes in patients (pts) with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (Pembro; MK-3475) in KEYNOTE-012 – Muro K, et al

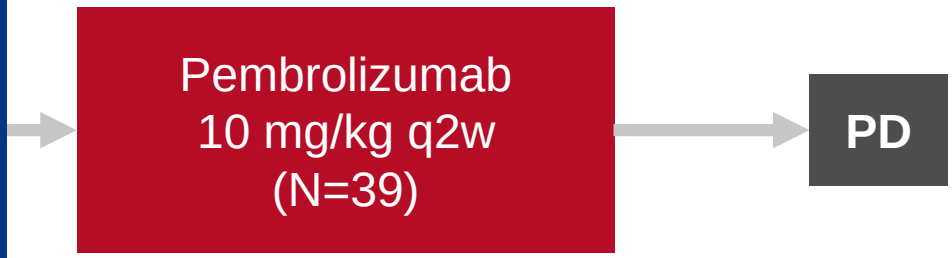
Study objective

- 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

Muro et al. J Clin Oncol 2015; 33 (suppl 3; abstr 3)

3: Relationship between PD-L1 expression and clinical outcomes in patients (pts) with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (Pembro; MK-3475) in KEYNOTE-012 – Muro K, 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 (%)		
Complete response	0	0
Partial response	8 (22.2)	13 (33.3)
Stable disease	5 (13.9)	5 (12.8)
Progressive disease	19 (52.8)	21 (53.8)

Muro et al. J Clin Oncol 2015; 33 (suppl 3; abstr 3)

3: Relationship between PD-L1 expression and clinical outcomes in patients (pts) with advanced gastric cancer treated with the anti-PD-1 monoclonal antibody pembrolizumab (Pembro; MK-3475) in KEYNOTE-012 – Muro K, 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

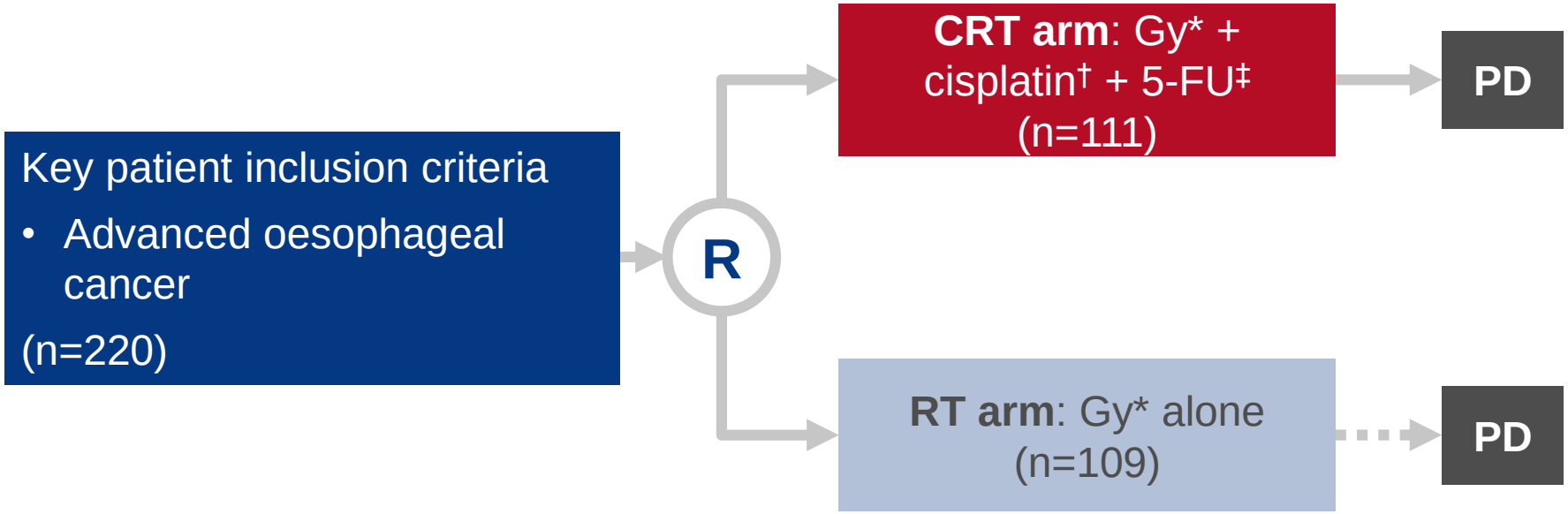
- **Pembrolizumab had an acceptable safety and tolerability profile in patients with PD-L1-positive advanced gastric cancer**
- **Pembrolizumab demonstrated a durable antitumour response in 22% of patients assessed by RECIST v1.1**
- **There was a trend towards improved overall response with higher PD-L1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

Muro et al. J Clin Oncol 2015; 33 (suppl 3; abstr 3)

6: Full report of the TROG 03.01, NCIC CTG ES2 multinational phase III study in advanced esophageal cancer comparing palliation of dysphagia and quality of life in patients treated with radiotherapy or chemoradiotherapy – Penniment MG, et al

Study objective

- To establish the optimal management (efficacy vs. toxicity) for symptom relief of advanced oesophageal cancer and to determine the effects of common cancer



PRIMARY ENDPOINT

- Dysphagia relief (assessed using Mellow scale)

SECONDARY ENDPOINT

- Dysphagia PFS

*35 Gy in 15 fractions or 30 Gy in 10 fractions; †80 mg/m^2 IV day 1 (or 20 mg/m^2 D1–4); ‡800 mg/m^2/day (D1–4)

Penniment et al. J Clin Oncol 2015; 33 (suppl 3; abstr 6)

6: Full report of the TROG 03.01, NCIC CTG ES2 multinational phase III study in advanced esophageal cancer comparing palliation of dysphagia and quality of life in patients treated with radiotherapy or chemoradiotherapy – Penniment MG, et al

Key results

	CRT arm	RT arm	p-value vs. RT arm
Dysphagia response* at Week 9, %	74	68	0.34
Dysphagia response* at Week 13, %	47	42	0.43
Median survival, days	203		

- Dysphagia PFS† and OS were not significantly different between the CRT vs. RT arms (p=0.65 and p=0.89, respectively)
- Toxicity increased with CRT vs. RT (nausea, p<0.01; vomiting, p<0.01)
- There was no significant difference in QoL between the two treatment arms
  - Improvement in QoL dysphagia domain: 50% with CRT arm vs. 64% with RT arm

Conclusions

- **With this schedule, CT added to RT did not significantly improve dysphagia**
- **CT increased toxicity and did not improve QoL vs. RT alone**
- **RT alone should remain SoC in patients with advanced oesophageal cancer**

*≥1 point reduction on the Mellow scale; †≥1 point reduction on the Mellow scale, stricture requiring intervention or death

Penniment et al. J Clin Oncol 2015; 33 (suppl 3; abstr 6)

OESOPHAGEAL AND GASTRIC CANCER

BIOMARKERS

7: Comprehensive genomic profiling (CGP) of advanced stage esophageal squamous cell carcinomas (ESCC) and esophageal adenocarcinomas (EAC) to reveal similarities and differences – Wang K, et al

Study objective

- To compare the genomic profiles of patients with advanced oesophageal SCC versus oesophageal ADC, in order to identify potential therapeutic targets

Study design

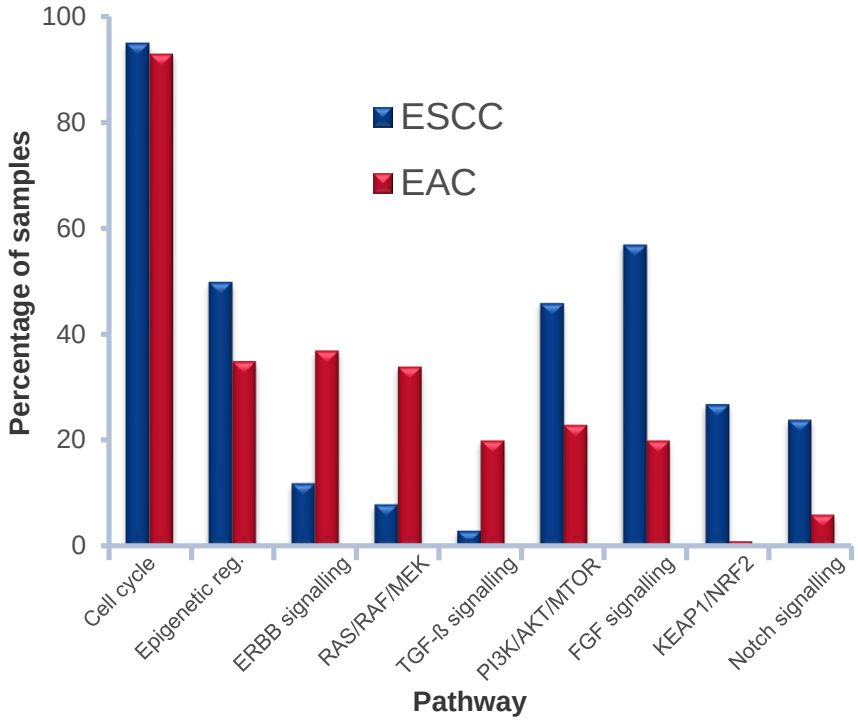
- DNA was extracted from FFPE sections (~40 μ) from patients with advanced (Stage III/IV) oesophageal SCC (N=71) and oesophageal ADC (N=231)
- Comprehensive genomic profiling was performed for all coding exons of 236 cancer-related genes and 19 genes that are frequently rearranged in cancer, in order to identify genomic alterations
- Clinically relevant genomic alterations (CRGA) were defined as genomic alterations (GA) linked to drugs currently on the market or under evaluation in clinical trials

Wang et al. J Clin Oncol 2015; 33 (suppl 3; abstr 7)

7: Comprehensive genomic profiling (CGP) of advanced stage esophageal squamous cell carcinomas (ESCC) and esophageal adenocarcinomas (EAC) to reveal similarities and differences – Wang K, et al

Key results

CRGA*	SCC, %	ADC, %	p-value
ERBB2	3	23	<0.0001
KRAS	6	23	0.0008
SMAD4	1	14	0.002
PIK3CA	24	10	0.004
CCND1	42	13	<0.0001
NFE2L2	24	1	<0.0001
NOTCH1	17	3	0.0001
SOX2	18	1	0.0001



Conclusions

- **Comprehensive genomic profiling can identify potential CRGA in oesophageal SCC and ADC and could potentially guide decisions for targeted therapies**
- **Oesophageal SCC and ADC share high frequencies of GA and CRGA**
  - **PI3K/mTOR/Notch pathway genes are significantly enriched in SCC**
  - **RAS/MEK pathway genes are significantly enriched in ADC**

*p<0.01 are listed. CRGA, clinically relevant genomic alteration; GA, genomic alteration

Wang et al. J Clin Oncol 2015; 33 (suppl 3; abstr 7)

8: Identification of the gastric microbiome from endoscopic biopsy samples using whole genome sequencing – Zhang C, et al

Study objective

- To investigate the composition of the gastric microbiome in patients with gastric cancer and *H. pylori* infection using whole genome sequencing

Study design

- Patients undergoing upper endoscopy with gastric cancer and either active or prior *H. pylori* infection were included
- Endoscopic biopsy samples (N=15) from the antrum, proximal body and fundus were obtained from 10 patients
- Whole genome sequencing was performed using Illumina TruSeq DNA sample preparation kit and Illumina Hi Seq 2500 platform
- All positive *H. pylori* positive samples were validated by qPCR

NSAID, nonsteroidal anti-inflammatory drugs

Zhang et al. J Clin Oncol 2015; 33 (suppl 3; abstr 8)

8: Identification of the gastric microbiome from endoscopic biopsy samples using whole genome sequencing – Zhang C, et al

Key results

- Eight patients had viable *H. pylori* and surprisingly, *H. pylori* was identified in previously treated patients
- Out of 37 gastric cancer tumour samples and matched normal samples from the TCGA study, 38% of them were *H. pylori* positive
  - This result is a novel discovery that was not reported in the TCGA study*

Conclusions

- **This is the first study to show detailed unbiased microbiome detection using whole genome sequencing in patients with gastric cancer**
- **Results indicate that standard treatment does not always eradicate *H. pylori***
  - **This may explain why *H. pylori* treatment fails to reduce cancer risk**
- **~40% of gastric cancers have evidence of persistent *H. pylori* bacterial content**

*Cancer Genome Atlas Research Network. Nature 2014; 513: 202–9

Zhang et al. J Clin Oncol 2015; 33 (suppl 3; abstr 8)

HEPATOCELLULAR CARCINOMA

236: New prognostic staging system from the multivariate survival analysis (MVA) of the patients with unresectable hepatocellular carcinoma (HCC) treated with doxorubicin drug eluting beads transarterial chemoembolization (DEB TACE) – Prajapati HJ, et al

Study objective

- To evaluate OS and independent prognostic factors of survival in patients with unresectable HCC treated with DEB TACE, and to develop a staging system from multivariate analysis (MVA) of survival and compare it with other staging systems

Study design

- A total of 420 unresectable patients with HCC, who received DEB TACE between December 2005 to March 2013, were evaluated
- Survival was analysed according to different staging systems from the time of the first DEB TACE
- The staging system was constructed from the survival analyses

DEB TACE, doxorubicin drug eluting beads transarterial chemoembolisation; HCC, hepatocellular carcinoma

Prajapati et al. J Clin Oncol 2015; 33 (suppl 3; abstr 236)

236: New prognostic staging system from the multivariate survival analysis (MVA) of the patients with unresectable hepatocellular carcinoma (HCC) treated with doxorubicin drug eluting beads transarterial chemoembolization (DEB TACE) – Prajapati HJ, et al

Key results

- Based upon the prognostic factors, CIS staging system was constructed and established
  - The median OS according to CIS stage I (score 0 or 1; 26.7% of patients), stage II (score 2 or 3; 40.2%), stage III (score 4–6; 25%) and stage IV (score ≥7; 8.1%) were 40.2, 24, 10.6 and 2.6 months, respectively (all p<0.0001)

Number	Variables/Scores	0	1	2
1	Child Pugh Class	A	B	C
2	ECOG PS	0	1	>1
3	Size of the index tumour	<4 cm	4–8 cm	>8 cm
4	Number of tumours	≤3	>3	
5	Portal vein invasion	Absent	Small vein invasion	Large vein invasion
6	Extra-hepatic metastases	Absent	Present	
7	Serum creatinine	<1.2 mg/dL	≥1.2 mg/dL	
8	Serum alpha feto protein	<400 ng/dL	≥400 ng/dL	

Conclusions

- **CIS is a new prognostic staging system for patients with advanced unresectable HCC after DEB TACE that is based on MVA of survival**

CIS, clinical, imaging and serum examination

Prajapati et al. J Clin Oncol 2015; 33 (suppl 3; abstr 236)

237: Phase II study of front-line dovitinib (TKI258) versus sorafenib in patients (pts) with advanced hepatocellular carcinoma (HCC) – Cheng AL, et al

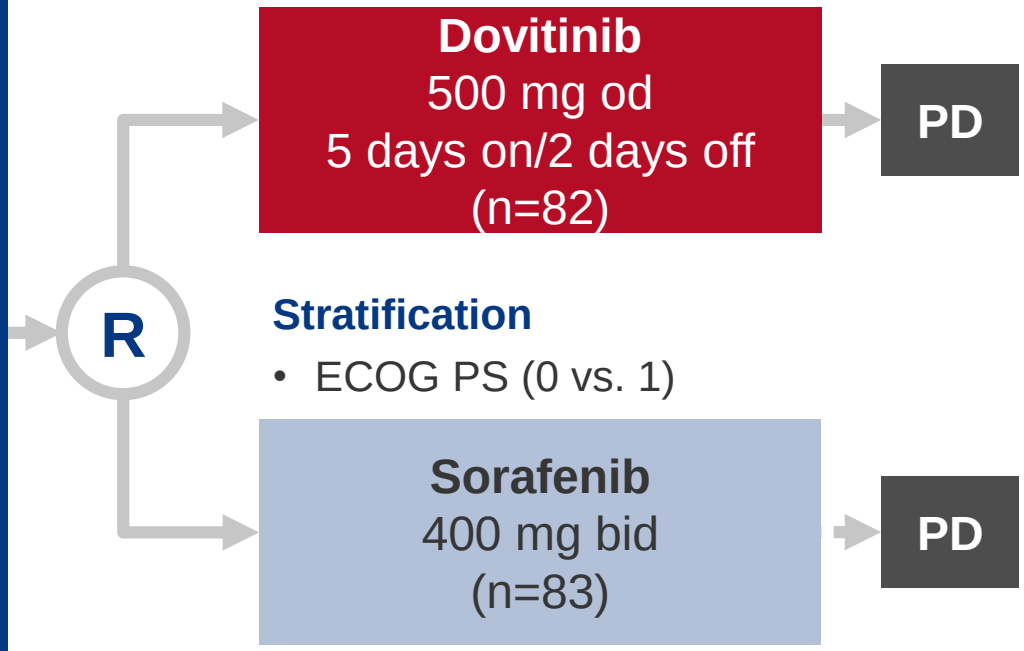
Study objective

- To evaluate the activity of dovitinib versus sorafenib as a first-line treatment in patients with advanced HCC

Key patient inclusion criteria

- Advanced HCC (stage B or C)
- No prior systemic therapy for HCC
- ECOG PS 0–1
- ≥1 measurable lesion per RECIST v1.1
- Child-Pugh Class A (5–6 points) with no encephalopathy

(n=165)



PRIMARY ENDPOINT

- OS

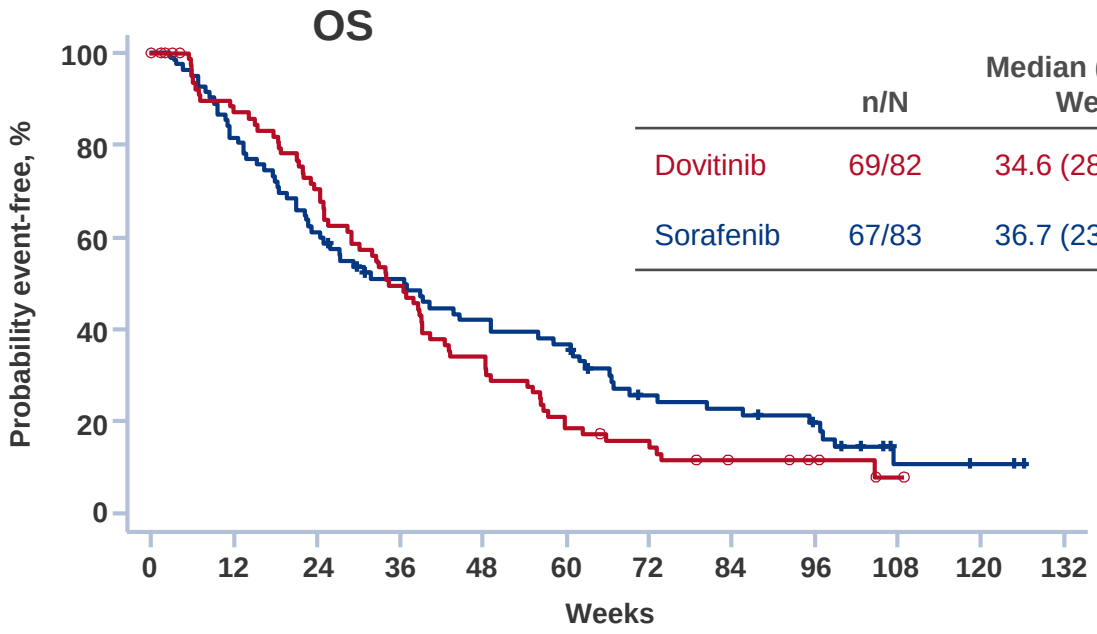
SECONDARY ENDPOINTS

- TTP, disease control rate, time to definitive deterioration in ECOG PS, safety, PK

Cheng et al. J Clin Oncol 2015; 33 (suppl 3; abstr 237)

237: Phase II study of front-line dovitinib (TKI258) versus sorafenib in patients (pts) with advanced hepatocellular carcinoma (HCC) – Cheng AL, et al

Key results



	n/N	Median (95% CI), Weeks	Hazard Ratio (95% CI)
Dovitinib	69/82	34.6 (28.6, 39.4)	1.27 (0.90, 1.79)
Sorafenib	67/83	36.7 (23.3, 49.3)	

- TTP and disease control rate were similar between the two treatment arms
- Median OS tended to be associated with sVEGFR1 and HGF baseline levels for both dovitinib and sorafenib, but only achieved significance for dovitinib
- Hepatic function did not affect dovitinib exposure

Cheng et al. J Clin Oncol 2015; 33 (suppl 3; abstr 237)

237: Phase II study of front-line dovitinib (TKI258) versus sorafenib in patients (pts) with advanced hepatocellular carcinoma (HCC) – Cheng AL, et al

Key results

AEs of any grade occurring in ≥30% in either group , n (%)	Dovitinib (n=79)			Sorafenib (n=83)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Diarrhoea	49 (62)	9 (11)	0	35 (42)	1 (1)	0
Decreased appetite	34 (43)	6 (8)	0	26 (31)	4 (5)	0
Nausea	32 (41)	4 (5)	0	16 (19)	0	0
Vomiting	32 (41)	1 (1)	0	10 (12)	1 (1)	0
Fatigue	28 (35)	11 (14)	0	13 (16)	2 (2)	0
Rash	27 (34)	1 (1)	0	18 (22)	2 (2)	0
Pyrexia	24 (30)	1 (1)	0	23 (28)	1 (1)	0
Palmar-plantar erythodysesthesia syndrome	11 (4)	1 (1)	0	55 (66)	13 (16)	0

Conclusions

- **Dovitinib showed no greater activity over sorafenib as a first-line therapy in patients with advanced HCC**
- **The dovitinib safety profile was similar to that observed in other trials**
- **Significant association of median OS with sVEGFR1 and HGF baseline plasma levels for dovitinib**

Cheng et al. J Clin Oncol 2015; 33 (suppl 3; abstr 237)

238: Randomized phase II trial comparing the efficacy and safety of nintedanib versus sorafenib in patients with advanced hepatocellular carcinoma (HCC) – Palmer DH, et al

Study objective

- To investigate the efficacy and safety of nintedanib, a triple angiokinase inhibitor of VEGFR, PDGFR and FGFR*, vs. sorafenib in patients with advanced HCC

Key patient inclusion criteria

- Unresectable/metastatic HCC
- No previous systemic therapy for HCC
- ECOG PS ≤2
- Child-Pugh class A
- ALT or AST levels ≤2 x ULN

(n=93)

R 2:1

Nintedanib 200 mg bid continuously† (n=62) → PD

Stratification

- Macrovascular invasion and/or extrahepatic spread vs. no invasion or spread

Sorafenib 400 mg bid continuously† (n=31) → PD

PRIMARY ENDPOINT

- TTP (central review as per RECIST 1.0)

SECONDARY ENDPOINTS

- OS, PFS and ORR (central independent review as per RECIST 1.0), TTP (investigator assessment), safety

*Also targets RET, Flt3 and Src; †28-day cycles

Palmer et al. J Clin Oncol 2015; 33 (suppl 3; abstr 238)

238: Randomized phase II trial comparing the efficacy and safety of nintedanib versus sorafenib in patients with advanced hepatocellular carcinoma (HCC) – Palmer DH, et al

Key results

	Nintedanib (N=62)	Sorafenib (N=31)
mTTP, months	5.5	4.6
HR (95% CI)	1.44 (0.81, 2.57)	
OS, months	11.9	11.4
HR (95% CI)	0.88 (0.52, 1.47)	
PFS, months	5.3	3.9
HR (95% CI)	1.35 (0.78, 2.34)	
Disease control rate, n (%)	51 (82.3)	28 (90.3)
ORR	1 (1.6)	2 (6.5)
CR	0	0
PR	1 (1.6)	2 (6.5)
SD	50 (80.6)	26 (83.9)
DP	8 (12.9)	1 (3.2)
Not evaluable/unknown	3 (4.8)	2 (6.5)

Palmer et al. J Clin Oncol 2015; 33 (suppl 3; abstr 238)

238: Randomized phase II trial comparing the efficacy and safety of nintedanib versus sorafenib in patients with advanced hepatocellular carcinoma (HCC) – Palmer DH, et al

Key results (cont.)

- Serious AEs: 54.8% with nintedanib vs. 45.2% with sorafenib
- AEs leading to discontinuation: 45.2% with nintedanib vs. 22.6% with sorafenib

AEs of Grade ≥3 (≥5% in either group), N (%)	Nintedanib (N=62)	Sorafenib (N=31)
Diarrhoea	8 (12.9)	1 (3.2)
Fatigue*	7 (11.3)	2 (6.5)
Increased AST	7 (11.3)	1 (3.2)
Increased ALT	5 (8.1)	2 (6.5)
Hepatic encephalopathy	5 (8.1)	1 (3.2)
Anaemia	4 (6.5)	1 (3.2)
Malignant neoplasm progression	2 (3.2)	3 (9.7)
Thrombocytopenia	1 (1.6)	3 (9.7)
Skin reaction	1 (1.6)	2 (6.5)
Hand-foot syndrome	0	7 (22.6)

Conclusions

- **Nintedanib showed similar efficacy to sorafenib in terms of TTP, OS, PFS and ORR**
- **Nintedanib had a manageable safety profile**
- **Further studies of nintedanib are warranted in patients with advanced HCC**

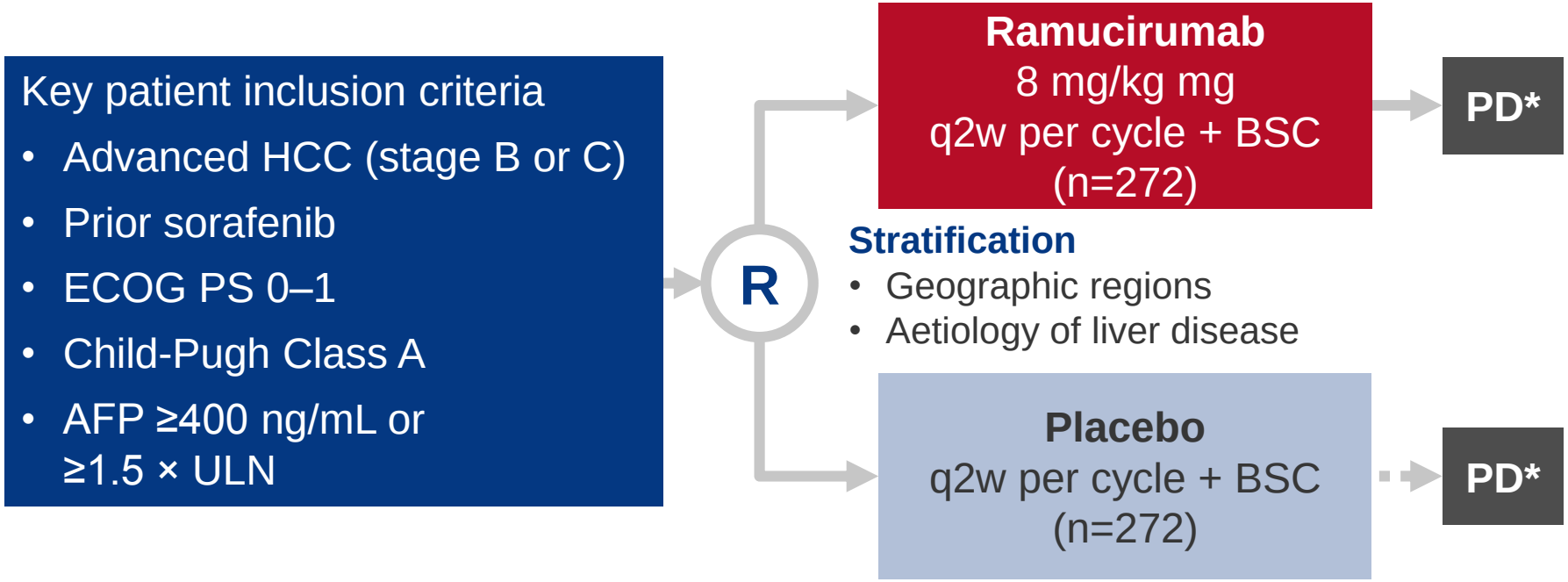
*Defined as fatigue, lethargy, asthenia and malaise

Palmer et al. J Clin Oncol 2015; 33 (suppl 3; abstr 238)

232: Ramucirumab (RAM) as second-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC): Analysis of patients with elevated α-fetoprotein (AFP) from the randomized phase III REACH study – Zhu AX, et al

Study objective

- To evaluate the efficacy and safety of single agent ramucirumab in a subgroup of patients with elevated AFP and advanced HCC after prior sorafenib therapy



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- PFS, TTP, ORR, safety, PROs

*Or unacceptable toxicity

Zhu et al. J Clin Oncol 2015; 33 (suppl 3; abstr 232)

232: Ramucirumab (RAM) as second-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC): Analysis of patients with elevated α-fetoprotein (AFP) from the randomized phase III REACH study – Zhu AX, et al

Key results

AFP ≥400 ng/mL	Ramucirumab (n=119)	Placebo (n=131)
Months, median	7.8	4.2
95% CI	5.8, 9.3	3.7, 4.8
HR (95% CI)	0.674 (0.508, 0.895)	
p-value (log-rank)	0.0059	

AFP <400 ng/mL	Ramucirumab (n=160)	Placebo (n=150)
Months, median	10.1	11.8
95% CI	8.7, 12.3	9.9, 13.1
HR (95% CI)	1.093 (0.836, 1.428)	
p-value (log-rank)	0.5059	

- In patients with baseline AFP ≥1.5 x ULN, median OS was 8.6 vs. 5.7 months for ramucirumab vs. placebo (HR 0.749; 95% CI 0.603, 0.930 [p=0.0088])
- Ramucirumab was well tolerated with an acceptable tolerability profile

Conclusions

- **Clinically meaningful improvements in OS were observed in patients with a baseline AFP ≥400 ng/mL or ≥1.5 × ULN**
- **Additional analyses showed that ramucirumab provided a consistent OS benefit for patients with baseline AFP over a wide range of values above the normal range**
- **Baseline AFP may be a predictive marker of OS benefit for ramucirumab**

Zhu et al. J Clin Oncol 2015; 33 (suppl 3; abstr 232)

230: *eNOS* polymorphisms in relation to outcome in advanced HCC patients receiving sorafenib – Casadei Gardini A, et al

Study objective

- To determine the prognostic and predictive role of endothelial nitric oxide synthase (*eNOS*) polymorphisms in response to sorafenib treatment in patients with advanced HCC

Study design

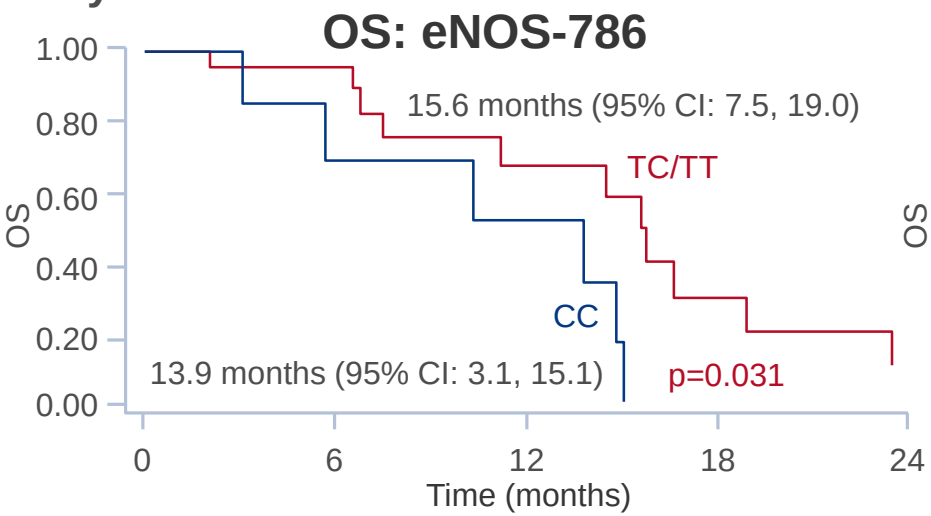
- From a database of 257 patients (cancer registry AVR), 54 patients were selected who received sorafenib
- Peripheral blood samples were analysed by PCR to identify the following *eNOS* polymorphisms:
  - eNOS-786 (N=29)
  - eNOS VNTR (N=21)
  - eNOS-786 (N=32)

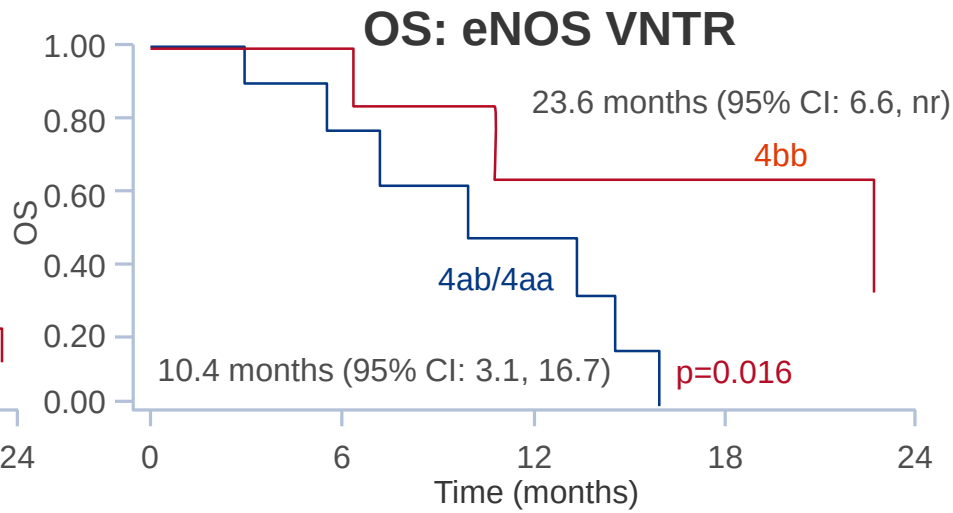
eNOS, endothelial nitric oxide synthase

Casadei Gardini et al. J Clin Oncol 2015; 33 (suppl 3; abstr 230)

230: *eNOS* polymorphisms in relation to outcome in advanced HCC patients receiving sorafenib – Casadei Gardini A, et al

Key results





- The T allele of eNOS-786 was associated with better OS than the CC allele (**Left Fig.**)
  - There was no significant difference in PFS (5.2 vs. 5.7 months, respectively; p=0.494)
- The 4bb allele of eNOS VNTR was associated with better OS than the 4ab/4aa allele (**Right Fig.**)
  - There was no significant difference in PFS (4.6 vs. 5.8 months, respectively; p=0.982)
- There were no significant differences in OS or PFS for the GG vs. GT/TT alleles of eNOS-894 (OS, p=0.759; PFS, p=0.118)

Conclusion

- **eNOS VNTR and eNOS-786 may be prognostic markers in patients with advanced HCC treated with sorafenib**

Casadei Gardini et al. J Clin Oncol 2015; 33 (suppl 3; abstr 230)

PANCREATIC CANCER

235: Prognosis model for overall survival in locally advanced unresectable pancreatic carcinoma: An ancillary study of the LAP 07 trial – Vernerey D, et al

Study objective

- To establish the first prognostic model for OS in locally advanced pancreatic cancer (LAPC) using the full spectrum of parameters currently available at diagnosis

Study design

- 442 LAPC patients were recruited from LAP 07, an international multicentre randomised phase III trial (NCT00634725); OS was estimated using the Kaplan Meier method
- 30 baseline variables were evaluated in univariate and multivariate analyses as prognostic factors for OS, including
  - demographic: age, sex
  - cancer history: site of primary tumour, histologic grade, regional lymph node, vascular invasion
  - clinical: WHO status, blood pressure, diarrhoea, pain, jaundice, BMI, weight loss
  - biological: neutrophils, haemoglobin, platelets, creatinine clearance, albumin, CA 19-9
  - radiological: tumour size
- A prognostic score and nomogram were developed based on the identified prognostic factors in the final model

Vernerey et al. J Clin Oncol 2015; 33 (suppl 3; abstr 235)
Presented by Franck Bonnetain

235: Prognosis model for overall survival in locally advanced unresectable pancreatic carcinoma: An ancillary study of the LAP 07 trial – Vernerey D, et al

Key results

- Five independent prognostic factors identified in multivariate analysis (n=358) for OS were: **age at diagnosis** (HR 1.01; 95% CI 1.00, 1.03; p=0.0478); **pain** (HR 1.29; 95% CI 1.02, 1.63; p=0.0317), **albumin** (HR 0.96; 95% CI 0.94, 0.98; p=0.0006), **RECIST tumour size** (HR 1.01; 95% CI 1.00, 1.02; p=0.0214) and **CA 19-9** (HR 1.17; 95% CI 1.05, 1.31; p=0.0056)
- Harrell's C-statistic for the final model was 0.60 (95% bootstrap CI 0.57, 0.64)
- A prognostic score between 0 and 5 was then calculated for each patient
- Three risk-groups for death were identified (p<0.0001 using log rank global test)
  - **low risk** (n=84; median OS time = **15.4 mo** [95% CI 12.4, 18.5]; reference group)
  - **intermediate risk** (n=263; median OS time = **12.8 mo** [95% CI 11.5, 14.3])
  - **high risk** (n=11; median OS time = **4.5 mo** [95% CI 2.3, 9.9])

Conclusions

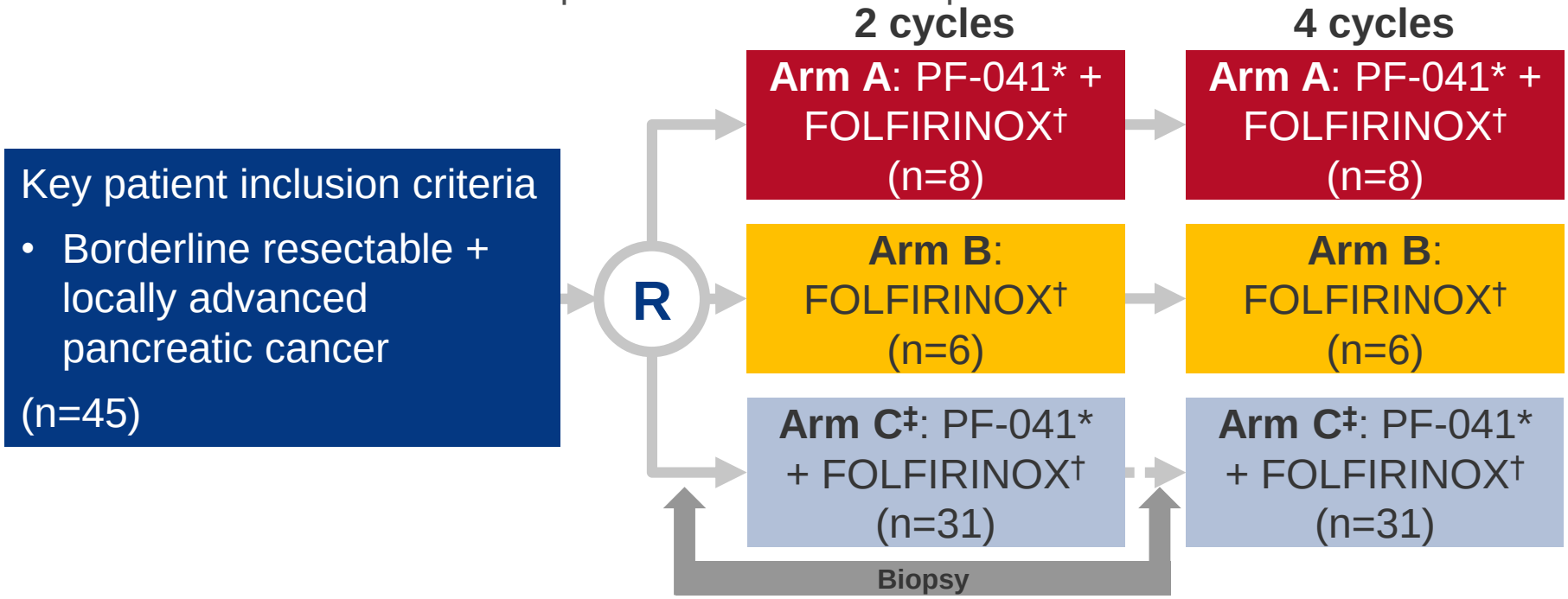
- **Five independent prognostic factors and three patient profiles were identified with clear-cut differences in OS**
- **This prognostic score and nomogram of risk stratification may help guide clinical management of patients and the design of future clinical trials**

Vernerey et al. J Clin Oncol 2015; 33 (suppl 3; abstr 235)
Presented by Franck Bonnetain

338: Phase IB study of FOLFIRINOX plus PF-04136309 in patients with borderline resectable and locally advanced pancreatic adenocarcinoma (PC) – Wang-Gillam A, et al

Study objective

To investigate the safety and efficacy of the CCR2 antagonist PF-04136309 (PF-041) in combination with FOLFIRINOX in patients with advanced pancreatic cancer



PRIMARY ENDPOINT

- Maximum tolerated dose

SECONDARY ENDPOINTS

- Safety, toxicity, efficacy

*500 mg bid; †Oxaliplatin 85 mg/m^2; irinotecan 180 mg/m^2, 5-FU 400 mg/m^2 bolus then 2,400 mg/m^2 over 46 hours, leucovorin 400 mg/m^2;
‡Expansion arm. CCR2, chemokine receptor 2

Wang-Gillam et al. J Clin Oncol 2015; 33 (suppl 3; abstr 338)

338: Phase IB study of FOLFIRINOX plus PF-04136309 in patients with borderline resectable and locally advanced pancreatic adenocarcinoma (PC) – Wang-Gillam A, et al

Key results

Treatment-related AEs, n (%)	PF-041 + FOLFIRINOX (Arms A + C*) (n=39)		FOLFIRINOX alone (Arm B) (n=6)	
	All grades	Grade ≥3	All grades	Grade ≥3
Haematological				
Neutropenia	28 (71.8)	26 (66.7)	6 (100.0)	6 (100.0)
Anaemia	38 (97.4)	1 (2.6)	5 (83.3)	2 (33.3)
Thrombocytopenia	18 (46.2)	1 (2.6)	4 (66.7)	0 (0)
Lymphopenia	22 (56.4)	2 (5.1)	3 (50.0)	1 (16.7)
Febrile neutropenia	5 (12.8)		1 (16.7)	
GCSF received†	19 (48.7)		3 (50)	
Non-haematological (≥60% all grades)				
Diarrhoea	22 (56.4)	5 (12.8)	6 (100.0)	2 (33.3)
Fatigue	26 (66.7)	1 (2.6)	1 (16.7)	0
Hypoalbuminaemia	26 (66.7)	1 (2.6)	4 (66.7)	1(16.7)
Hypokalaemia	25 (64.1)	8 (20.5)	4 (66.7)	3 (50.0)
Alopecia	24 (61.5)	0	4 (66.7)	0

*Expansion arm; †GCSF use was only allowed after completion of two therapy cycles

Wang-Gillam et al. J Clin Oncol 2015; 33 (suppl 3; abstr 338)

338: Phase IB study of FOLFIRINOX plus PF-04136309 in patients with borderline resectable and locally advanced pancreatic adenocarcinoma (PC) – Wang-Gillam A, et al

Key results (cont.)

- The proportion of patients completing 6 cycles of therapy was 75% for arm A, 33% for arm B and 78% for arm C*

Overall response, n (%)	PF-041 + FOLFIRINOX (Arms A + C*) (n=29)	FOLFIRINOX alone (Arm B) (n=4)	Historical control† FOLFIRINOX (n=18)
CR	**0**	**0**	**1 (6)**
PR	**14 (48)**	**0**	**5 (28)**
SD	14 (48)	3 (75)	9 (50)
PD	1 (4)	1 (25)	3 (17)

- 48.3% of patients treated with PF-041 + FOLFIRINOX had a decrease from baseline in best primary tumour response of ≥30%

Conclusions

- **PF-041 500 mg bid added to FOLFIRINOX is the recommended Phase II dose**
- **Toxicities were manageable with the most frequent AEs attributed to FOLFIRINOX**
- **PF-041 added to FOLFIRINOX should be explored in a large clinical study**

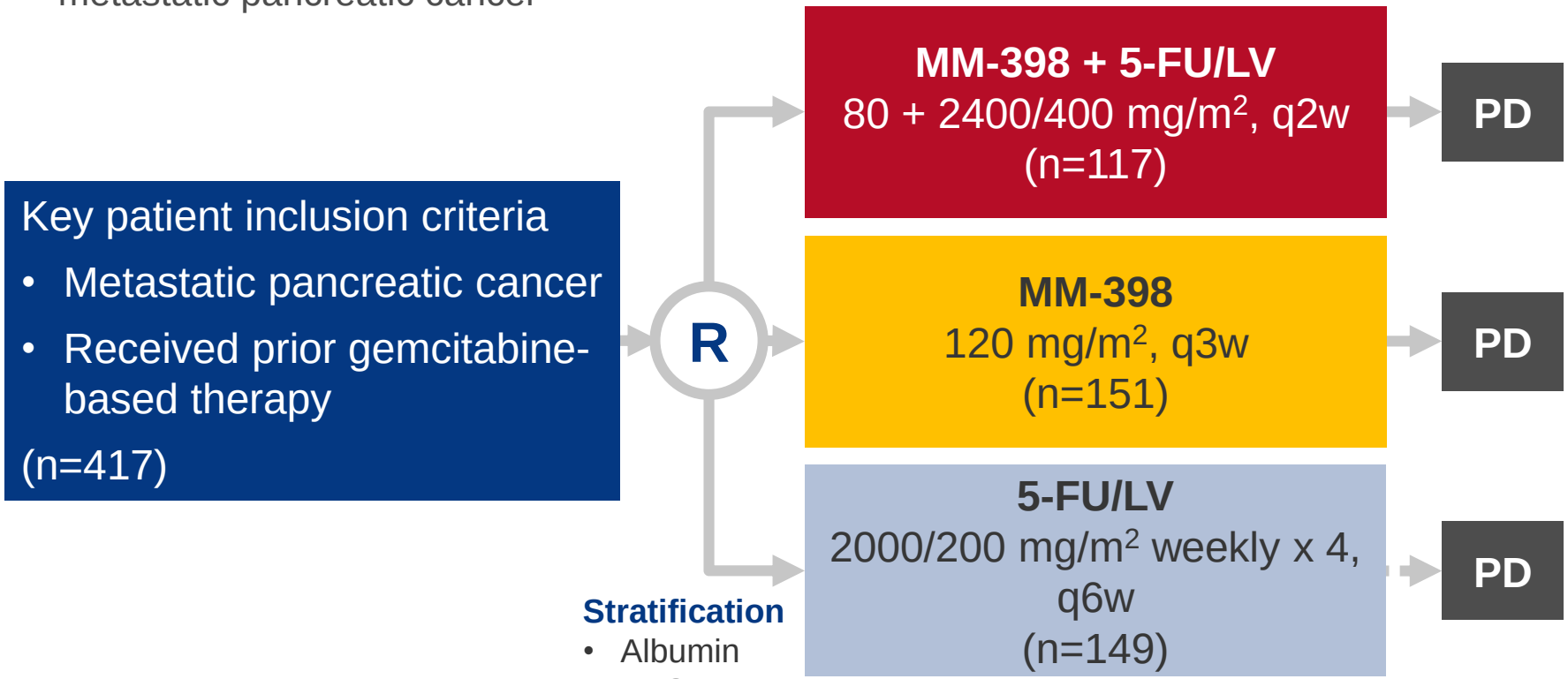
*Expansion arm; †Multi-institutional review on patients with borderline resectable + locally advanced pancreatic cancer

Wang-Gillam et al. J Clin Oncol 2015; 33 (suppl 3; abstr 338)

234: Expanded analyses of NAPOLI-1: Phase 3 study of MM-398 (nal-IRI), with or without fluorouracil and leucovorin, versus 5-fluorouracil and leucovorin, in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy – Chen LT, et al

Study objective

- To investigate the efficacy and safety of adding MM-398 to 5-FU and LV in patients with metastatic pancreatic cancer



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

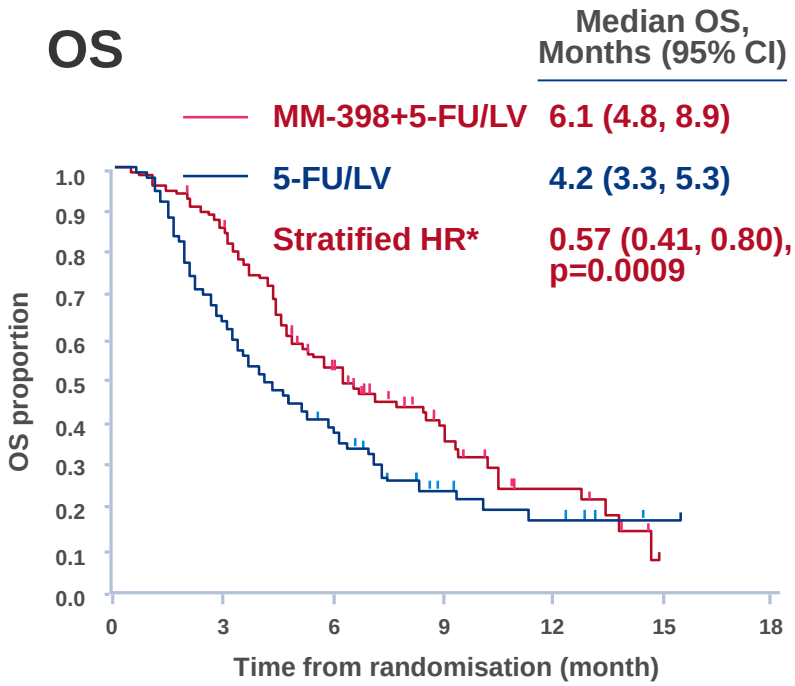
- PFS, ORR, CA19-9 response, safety

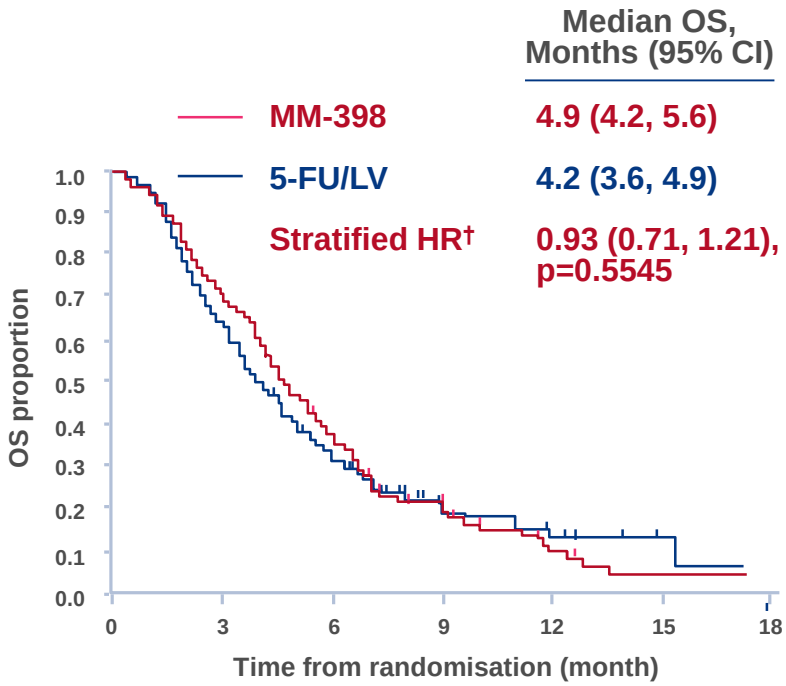
Chen et al. J Clin Oncol 2015; 33 (suppl 3; abstr 234)

234: Expanded analyses of NAPOLI-1: Phase 3 study of MM-398 (nal-IRI), with or without fluorouracil and leucovorin, versus 5-fluorouracil and leucovorin, in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy – Chen LT, et al

Key results

OS





- MM-398 + 5-FU/LV significantly increased PFS and ORR and provided a greater reduction in CA19-9 compared with 5-FU/LV
- MM-398 + 5-FU/LV demonstrated favourable outcomes for OS in prognostic subgroups, tumour characteristics and previous treatment vs. 5-FU/LV

*Unstratified HR 0.67 (95% CI 0.49, 0.92), p=0.0122;
**unstratified HR 0.99 (95% CI 0.77, 1.28), p=0.9416

Chen et al. J Clin Oncol 2015; 33 (suppl 3; abstr 234)

234: Expanded analyses of NAPOLI-1: Phase 3 study of MM-398 (nal-IRI), with or without fluorouracil and leucovorin, versus 5-fluorouracil and leucovorin, in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy – Chen LT, et al

Key results

	MM-398 + 5-FU/LV (n=117)	5-FU/LV (n=134)
Grade ≥3 non-haematological AEs occurring in >5% of patients (%)		
Fatigue	14	4
Diarrhoea	13	5
Vomiting	11	3
Nausea	8	3
Asthenia	8	7
Abdominal pain	7	6
Grade ≥3 haematological AEs based on laboratory values (%)		
Neutrophil count decreased	20	2
Haemoglobin decreased	6	5
Platelet count decreased	2	0

Conclusions

- **The addition of MM-398 to 5-FU/LV significantly improved OS, PFS, ORR and CA19-9 response compared with 5-FU/LV alone**
- **MM-398 alone showed no significant survival benefit over 5-FU/LV alone**
- **MM-398 + 5-FU/LV has a manageable safety profile**

Chen et al. J Clin Oncol 2015; 33 (suppl 3; abstr 234)

BILIARY TRACT CANCER

231: Comprehensive genomic profiling of biliary tract cancers reveals tumor-specific differences and a high frequency of clinically relevant genomic alterations – Ross JS, et al

Study objective

- To identify clinically relevant genomic alterations in biliary tract cancers including IHCCA, EHCCA and gallbladder cancer that could guide selection or development of targeted therapies

Study design

- DNA was extracted from 554 FFPE biliary tract cancer samples including IHCCA (n=412), EHCCA (n=57) and gallbladder carcinoma (n=85)
- Comprehensive genomic profiling was performed to identify genomic alterations for 315 cancer-related genes and 47 introns of 19 genes frequently rearranged in cancer
- Clinically relevant genomic alterations were defined as genomic alterations that were linked to anti-cancer drugs currently on the market or in clinical trials

IHCCA, intrahepatic cholangiocarcinoma; EHCCA, extrahepatic cholangiocarcinoma; FFPE, formalin-fixed paraffin embedded

Ross et al. J Clin Oncol 2015; 33 (suppl 3; abstr 231)

231: Comprehensive genomic profiling of biliary tract cancers reveals tumor-specific differences and a high frequency of clinically relevant genomic alterations – Ross JS, et al

Key results

Genomic alterations	IHCCA	EHCCA	Gall bladder cancer
Total genomic alterations/patient, n	3.6	4.4	4.0
Clinically relevant genomic alterations/patient, n	2.0	2.1	2.0
ERBB2 amplification, %	4	11	16
BRAF substitutions, %	5	3	1
KRAS substitutions, %	22	42	11
PI3KCA substitution, %	5	7	14
FGFR1–3 fusions + amplifications, %	11	0	3
CDKN2A/B loss, %	27	17	19
IDH1/2 substitutions, %	20	0	0
ARID1A alterations, %	18	12	13
MET amplification, %	2	0	1

Ross et al. J Clin Oncol 2015; 33 (suppl 3; abstr 231)

231: Comprehensive genomic profiling of biliary tract cancers reveals tumor-specific differences and a high frequency of clinically relevant genomic alterations – Ross JS, et al

Conclusions

- **Genomic alterations were identified in two thirds of patients with biliary tract cancers, which could potentially influence treatment and guide the selection of targeted therapies**
- **Comprehensive genomic profiling appears to have significant potential to maximise the identification of new treatment paradigms in patients with biliary tract cancers**

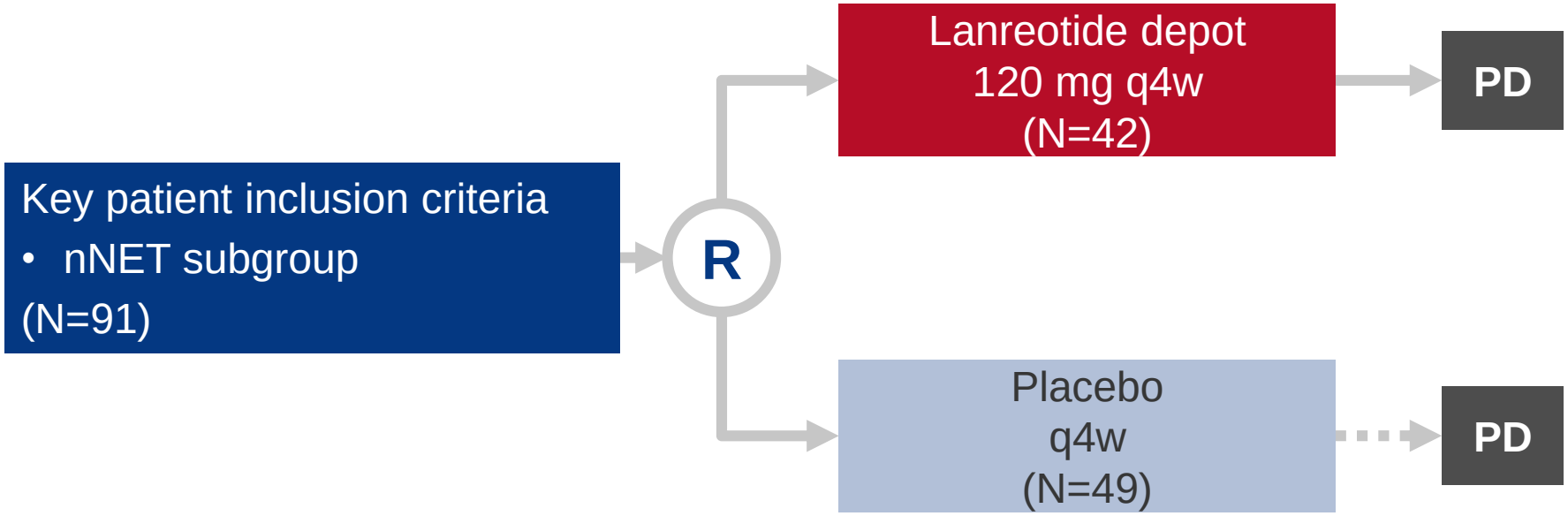
Ross et al. J Clin Oncol 2015; 33 (suppl 3; abstr 231)

PANCREATIC NEUROENDOCRINE TUMOURS

233: Effects of lanreotide autogel/depot (LAN) in pancreatic neuroendocrine tumors (pNETs): A subgroup analysis from the CLARINET study – Phan AT, et al

Study objective

- To evaluate the risk-benefit profile for lanreotide depot in the pNET subpopulation, using a planned subgroup analysis of prospective data, of the CLARINET study



PRIMARY ENDPOINT

- PFS

SECONDARY ENDPOINTS

- Response, safety

Phan et al. J Clin Oncol 2015; 33 (suppl 3; abstr 233)

233: Effects of lanreotide autogel/depot (LAN) in pancreatic neuroendocrine tumors (pNETs): A subgroup analysis from the CLARINET study – Phan AT, et al

Key results

- **Median PFS in the pNET subgroup was not reached at study end with lanreotide depot vs. 12.1 months** (95% CI 9.4, 18.3) **with placebo** (**HR 0.58**; 95% CI 0.32, 1.04): NS

Any AE, n (%)	Lanreotide depot 120 mg (N=42)	Placebo (N=49)
Any AE	37 (88)	43 (88)
Severe / moderate / mild	15 (36) / 19 (45) / 3 (7)	18 (37) / 20 (41) / 5 (10)
Any serious AE	12 (29)	21 (43)
Withdrawals due to AEs	2 (5)	2 (4)
Most common AEs		
Diarrhoea	18 (43)	18 (37)
Vomiting	13 (31)	3 (6)
Abdominal pain	9 (21)	8 (16)
Back pain	9 (21)	6 (12)

Conclusion

- **These findings suggest a positive risk-benefit profile for lanreotide depot as a first-line treatment for patients with metastatic pNETs with stable or progressive disease**

Phan et al. J Clin Oncol 2015; 33 (suppl 3; abstr 233)