GI SLIDE DECK 2017

Selected abstracts from:

european society of digestive oncology
esdo

Supported by Eli Lilly and Company.
Eli Lilly and Company has not influenced the content of this publication

Lilly

Letter from ESDO

DEAR COLLEAGUES

It is our 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 2017. This slide set specifically focuses on the **18th World Congress on Gastrointestinal Cancer 2017** and is available in English, French and Japanese.

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 that helps to educate and inspire further advancements in our roles as scientists, clinicians and educators. We 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.

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

Yours sincerely,

Eric Van Cutsem
Thomas Seufferlein
Côme Lepage
Wolff Schmiegel
Philippe Rougier
(honorary member)

Ulrich Güller
Thomas Grünberger
Tamara Matysiak-Budnik
Jaroslaw Regula
Jean-Luc Van Laethem

(ESDO Governing Board)

esdo

european society of digestive oncology

ESDO Medical Oncology Slide Deck
Editors 2017

COLORECTAL CANCERS



Prof Eric Van Cutsem	Digestive Oncology, University Hospitals, Leuven, Belgium
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 Laethem	Digestive Oncology, Erasme University Hospital, Brussels, Belgium
Prof Thomas Seufferlein	Clinic of Internal Medicine I, University of Ulm, Ulm, Germany

GASTRO-OESOPHAGEAL AND NEUROENDOCRINE TUMOURS


Emeritus Prof Philippe Rougier	University Hospital of Nantes, Nantes, France
Prof Côme Lepage	University Hospital & INSERM, Dijon, France

BIOMARKERS


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

esdo

Glossary

1L	first-line
2L	second-line
3L	third-line
7L	seventh-line
5FU	5-fluorouracil
AE	adverse event
AG	nab-paclitaxel + gemcitabine
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
BEV	bevacizumab
BOR	best overall response
CAPOX	capecitabine + oxaliplatin
CI	confidence interval
CK	creatinine kinase
CR	complete response
CRC	colorectal cancer
CT	chemotherapy
ctDNA	circulating DNA
D	day
DCR	disease control rate
ddPCR	droplet digital polymerase chain reaction
DFS	disease-free survival
DICOM	digital imaging and communications in medicine
DLT	dose-limiting toxicity
(mDoR	(median) duration of response
ECD	extracellular domain
ECF	epirubicin + cisplatin + 5-fluorouracil
ECX	epirubicin + cisplatin + capecitabine
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
FAS	full analysis set
FGF(R)	fibroblast growth factor (receptor)
FISH	fluorescence in situ hybridisation
FLOT	docetaxel + oxaliplatin + leucovorin + 5-fluorouracil
FOLFIRI	5-fluorouracil + irinotecan + folinic acid
FOLFOX	5-fluorouracil + oxaliplatin
FP	fluoropyrimidine
GEJ	gastro-oesophageal junction
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
HA	hyaluronan
HCC	hepatocular carcinoma
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
IHC	immunohistochemistry
IRCC	Institute for Cancer Research and Treatment
IRI	irinotecan
ITT	intent-to-treat
IV	intravenous
KPS	Karonofsky performance status
mCRC	metastatic colorectal cancer
MMR	mismatch repair
MSI	microsatellite instability
MTD	maximum tolerated dose
MUT	mutant
NA	not available
NE	not evaluable
NGS	next generation sequencing
NR	not reached
NS	non-significant
OG	oesophagogastric
OR	odds ratio
ORR	overall/objective response rate
(m)OS	(median) overall survival
PAG	PEGPH20 + nab-paclitaxel + gemcitabine
PD	progressive disease
PDAC	pancreatic ductal adenocarcinoma
PD-L1	programmed death-ligand 1
PEGPH20	pegylated recombinant human hyaluronidase
(m)PFS	(median) progression-free survival
PIGF	placental growth factor
PK	pharmacokinetics
PR	partial response
PS	performance status
q(2/3/4)w	every (2/3/4) week(s)
qd	once daily
QLQ-C30	quality of life questionnaire C30
qod	every other day
QoL	quality of life
R	randomised
RECIST	Response Evaluation Criteria In Solid Tumors
RFS	relapse-free survival
RP2D	recommended phase 2 dose
SAR	survival after relapse
SD	stable disease
SIRT	selective internal radiotherapy
SoC	standard of care
SQ	subcutaneously
TACE	transarterial chemoembolisation
TE	thromboembolic
TFS	time to failure of strategy
TRAE	treatment-related adverse event
TRR	tumour response rate
TTR	time to response
uPR	unconfirmed partial response
VEGF	vascular endothelial growth factor
WC	withdrawn consent
WHO	World Health Organisation
WT	wild type

Contents

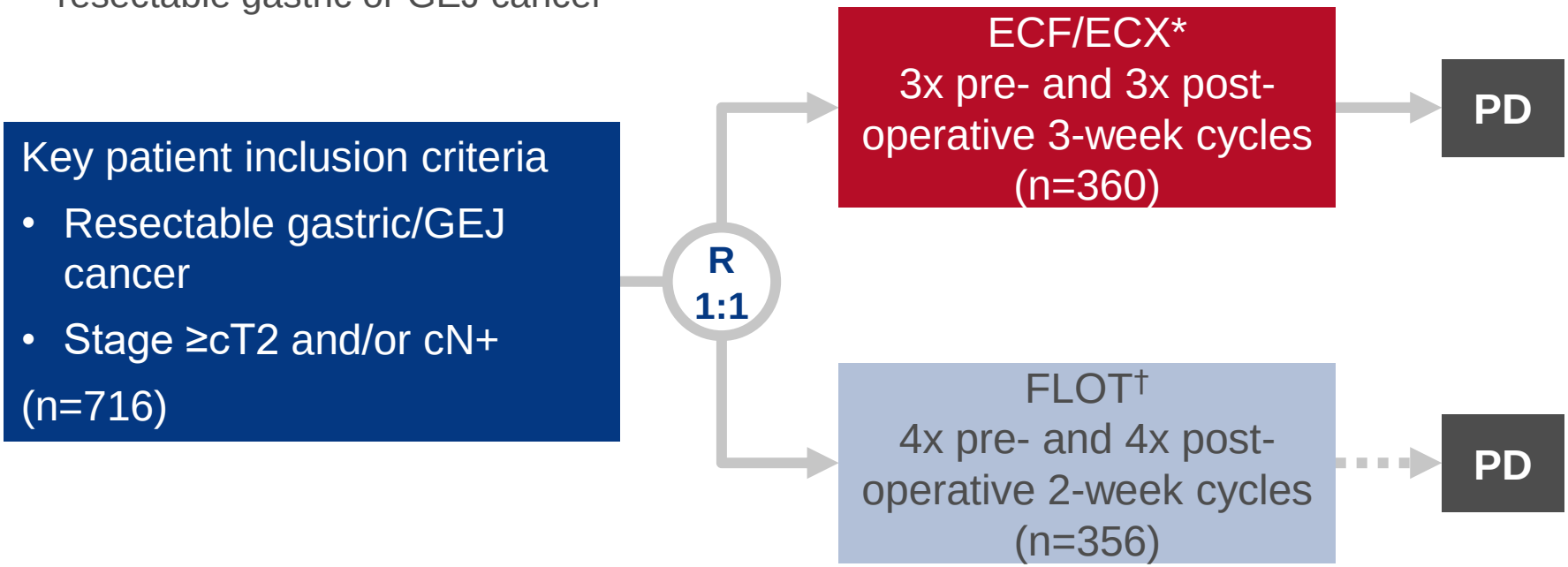
Note: To jump to a section, right click on the number and ‘Open Hyperlink’

CANCERS OF THE OESOPHAGUS AND STOMACH

LBA-008: Docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) as perioperative treatment of resectable gastric or gastroesophageal junction adenocarcinoma: The multicenter, randomized phase 3 FLOT4 trial (German Gastric Group at AIO) – Al-Batran S-E

Study objective

- To assess the efficacy and safety of perioperative ECF/ECX vs. FLOT for patients with resectable gastric or GEJ cancer



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- Resection rate, PFS, safety

*Epirubicin 50 mg/m^2 D1 + cisplatin 60 mg/m^2 D1 + 5FU 200 mg/m^2 continuous infusion or capecitabine 1250 mg/m^2 D1–21; †docetaxel 50 mg/m^2 + oxaliplatin 85 mg/m^2 + leucovorin 200 mg/m^2 + 5FU 2600 mg/m^2 24-hr infusion, all D1

Developed based on abstract only

Al-Batran S-E, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-008

LBA-008: Docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) as perioperative treatment of resectable gastric or gastroesophageal junction adenocarcinoma: The multicenter, randomized phase 3 FLOT4 trial (German Gastric Group at AIO) – Al-Batran S-E

Key results

Key efficacy outcomes	ECF/ECX	FLOT	HR (95%CI)	p-value
R0 resection rate, %	77	48	-	0.011
mOS, months	35	50	0.77 (0.63, 0.94)	0.012
mPFS, months	18	30	0.75 (0.62, 0.91)	0.004
3-year OS rate, %	48	57	-	-
Tumours ≤pT1, %	15	25	-	0.001

Morbidity and mortality, %	ECF/ECX	FLOT
Perioperative complications	50	51
30-day mortality	3	2
90-day mortality	8	5

Conclusion

- **In patients with resectable gastric or GEJ cancer, perioperative FLOT improved outcomes vs. ECF/ECX and may be considered as a new standard therapy in this setting**

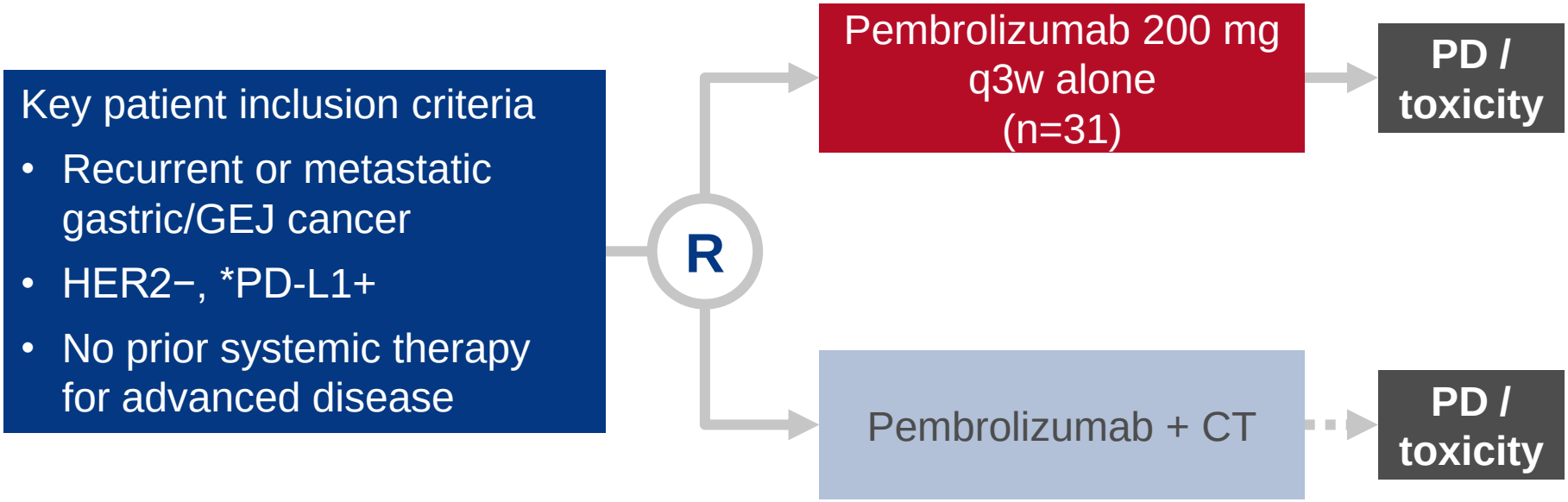
Developed based on abstract only

Al-Batran S-E, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-008

LBA-009: KEYNOTE-059 cohort 3: safety and efficacy of pembrolizumab monotherapy for first-line treatment of patients (pts) with PD-L1-positive advanced gastric/gastroesophageal (G/GEJ) cancer – Catenacci DV, et al

Study objective

- To evaluate the efficacy and safety of 1L pembrolizumab ± CT in patients with PD-L1+ advanced gastric or GEJ cancer (data from pembrolizumab monotherapy arm reported)



PRIMARY ENDPOINTS

- ORR, safety

SECONDARY ENDPOINTS

- DoR, PFS, OS

*PD-L1 combined positive score ≥1% (number of PD-L1 staining tumour cells, lymphocytes and macrophages divided by the total number of viable tumour cells x100)

Developed based on abstract only

Catenacci DV, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-009

LBA-009: KEYNOTE-059 cohort 3: safety and efficacy of pembrolizumab monotherapy for first-line treatment of patients (pts) with PD-L1-positive advanced gastric/gastroesophageal (G/GEJ) cancer – Catenacci DV, et al

Key results

Key efficacy outcomes (n=31)	
ORR, % (95%CI)	25.8 (11.9, 44.6)
CR, %	3.2
mDoR, % (range)	NR (2.1–13.7+)
mPFS, months (95%CI)	3.3 (2.0, 6.0)
mOS, months (95%CI)	NR (9.2, NE)
6-month OS rate, %	72.9
12-month OS rate, %	61.7

TRAEs (n=31)	
Any grade, n (%)	24 (77.4)
Grade 3–5, n (%)	7 (22.6)

Conclusion

- **In patients with PD-L1+ advanced gastric or GEJ cancer, pembrolizumab monotherapy showed promising anti-tumour activity with an acceptable safety profile as a 1L therapy**

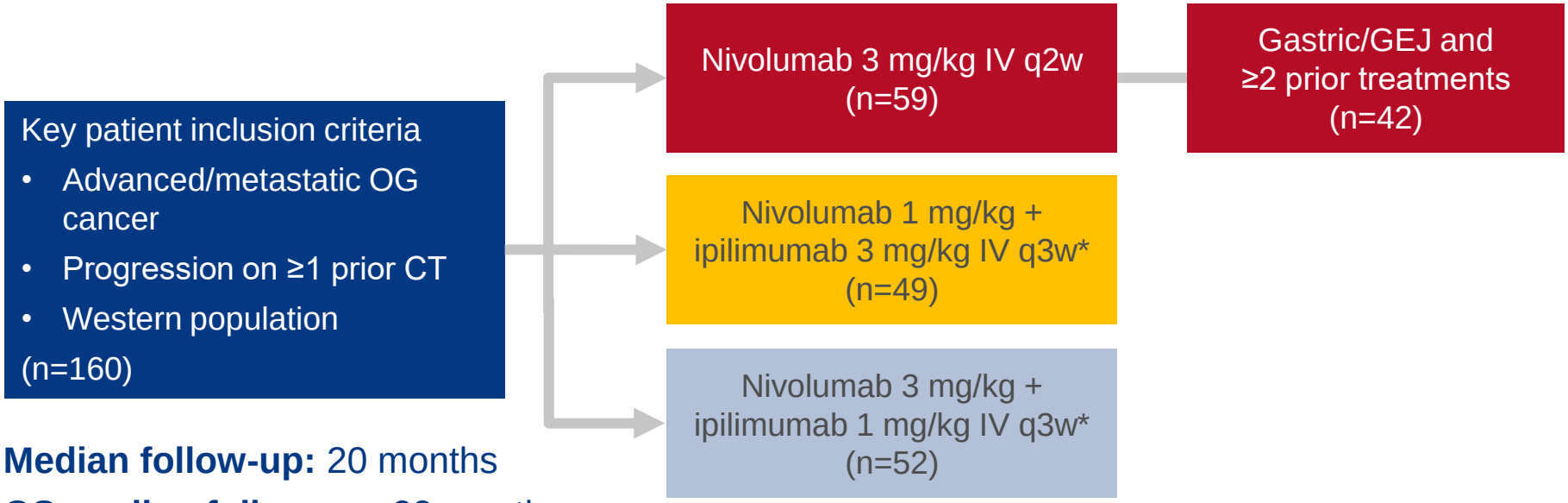
Developed based on abstract only

Catenacci DV, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-009

O-007: Nivolumab monotherapy in patients with advanced gastric of gastroesophageal junction (GEJ) cancer and 2 or more prior treatment regimens: Sub-analysis of the CheckMate 032 study – Ott P, et al

Study objective

- To investigate the safety and efficacy of nivolumab in a subset of patients with gastric/GEJ cancer and ≥2 prior treatment regimens from the CheckMate 032 study



Median follow-up: 20 months

OS median follow-up: 28 months

PRIMARY ENDPOINT

- ORR per RECIST v1.1

SECONDARY ENDPOINTS

- Safety, OS, PFS, TTR, DoR

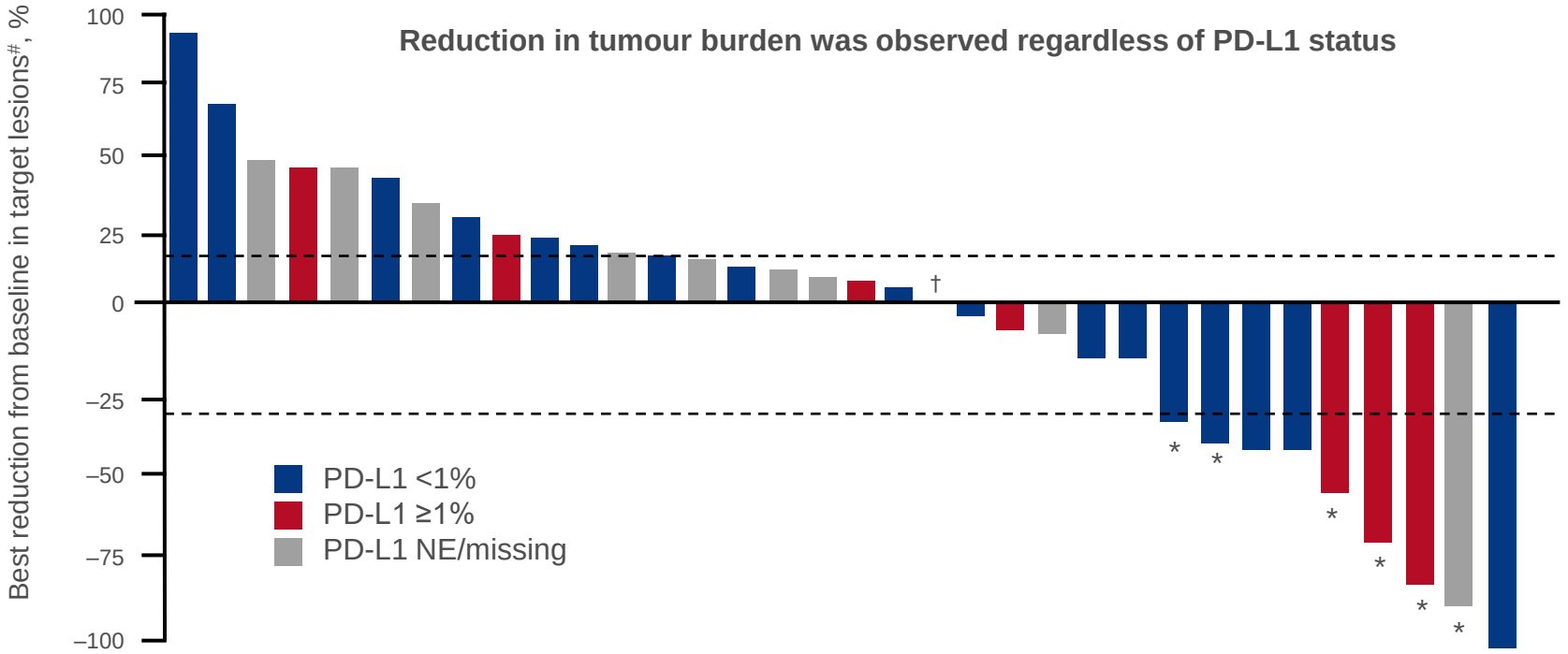
*Nivolumab + ipilimumab was administered for 4 cycles followed by nivolumab 3 mg/kg IV q2w

Ott P, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-007

O-007: Nivolumab monotherapy in patients with advanced gastric of gastroesophageal junction (GEJ) cancer and 2 or more prior treatment regimens: Sub-analysis of the CheckMate 032 study – Ott P, et al

Key results

Best reduction in tumour burden by PD-L1 status



Best reduction is based on evaluable target lesion measurements up to progression or start of subsequent therapy
*Patients with confirmed response (CR or PR)
†Patient who was PD-L1 ≥1 at baseline and had 0% best reduction in target lesion

#Investigator review

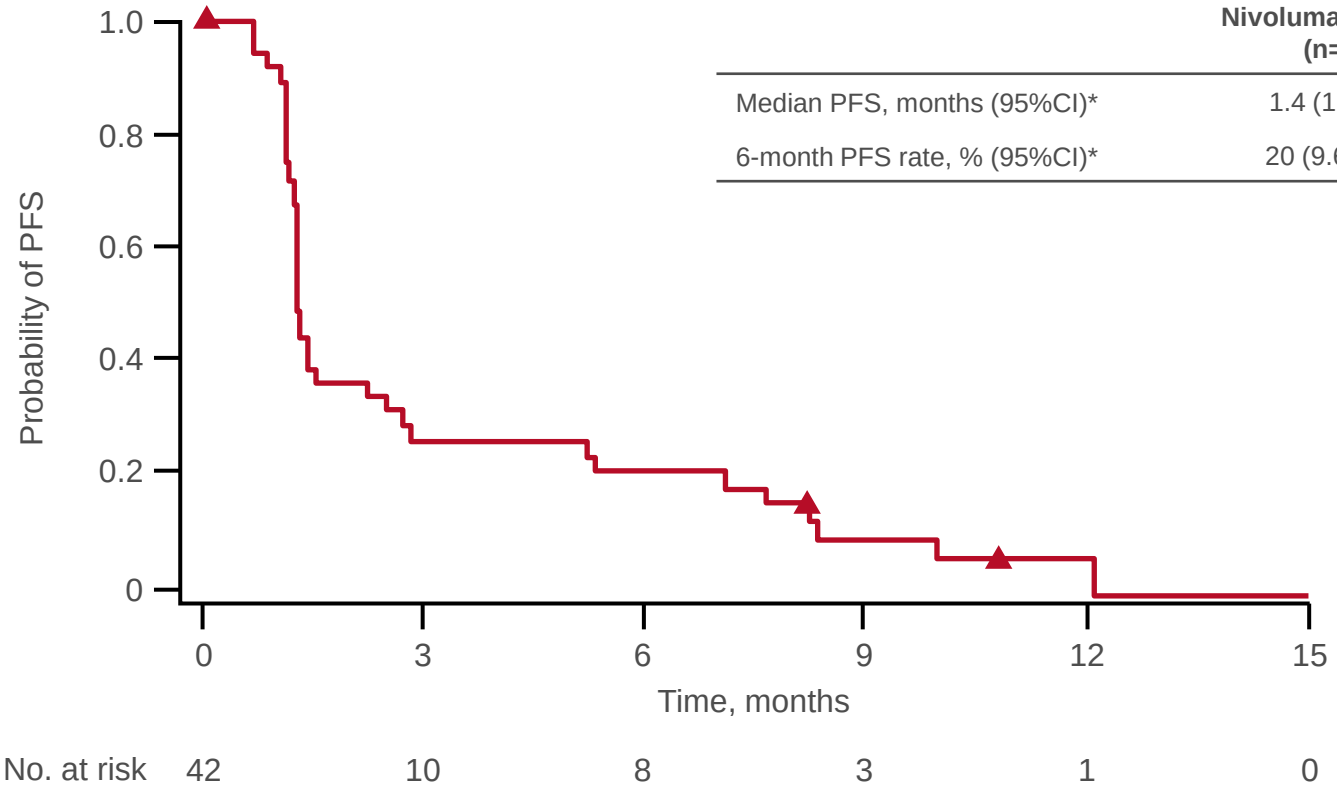
Ott P, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-007

O-007: Nivolumab monotherapy in patients with advanced gastric of gastroesophageal junction (GEJ) cancer and 2 or more prior treatment regimens: Sub-analysis of the CheckMate 032 study – Ott P, et al

Key results (cont.)

PFS

	Nivolumab 3 mg/kg (n=42)
Median PFS, months (95%CI)*	1.4 (1.3, 2.3)
6-month PFS rate, % (95%CI)*	20 (9.6, 34.2)



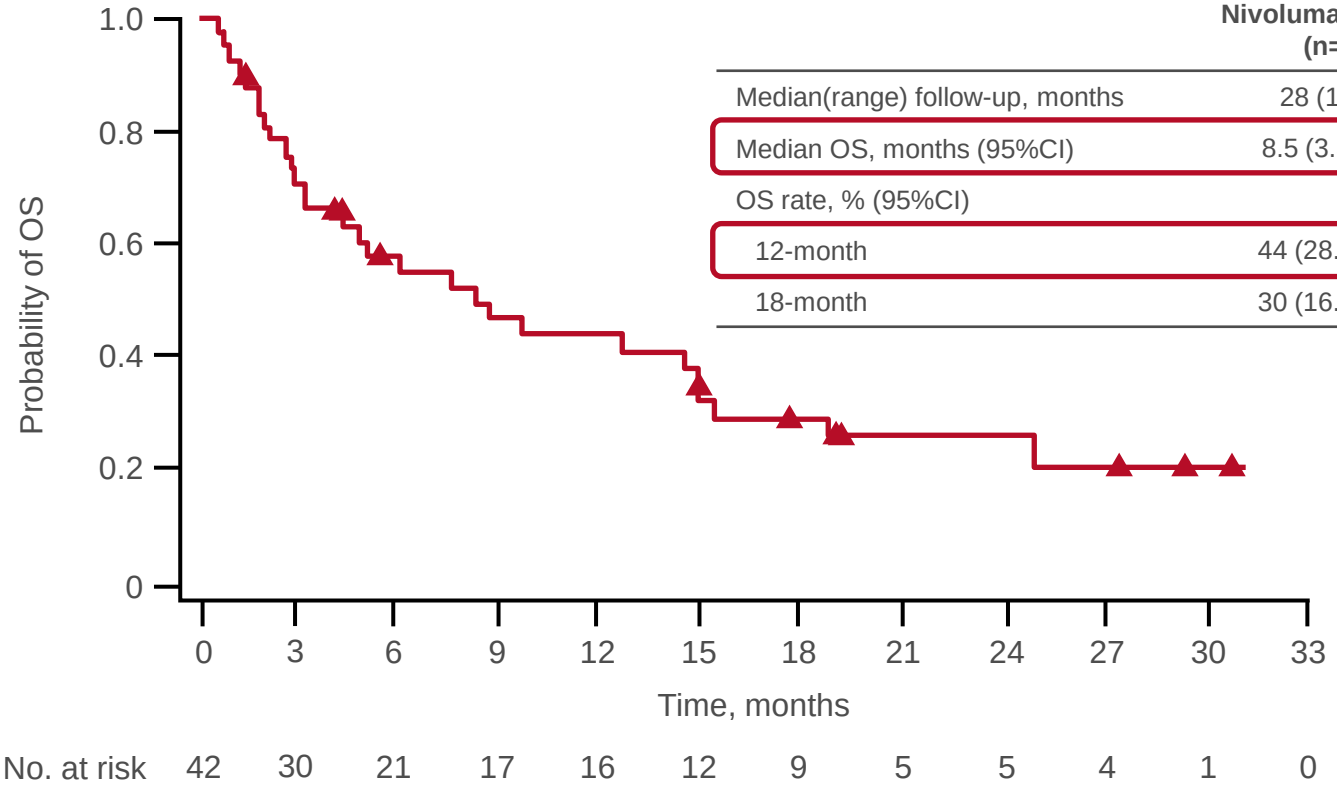
*Investigator review

Ott P, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-007

O-007: Nivolumab monotherapy in patients with advanced gastric of gastroesophageal junction (GEJ) cancer and 2 or more prior treatment regimens: Sub-analysis of the CheckMate 032 study – Ott P, et al

Key results (cont.)

OS



	Nivolumab 3 mg/kg (n=42)
Median(range) follow-up, months	28 (17–35)
Median OS, months (95%CI)	8.5 (3.3, 15.0)
OS rate, % (95%CI)	
12-month	44 (28.4, 59.0)
18-month	30 (16.2, 45.0)

Ott P, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-007

O-007: Nivolumab monotherapy in patients with advanced gastric of gastroesophageal junction (GEJ) cancer and 2 or more prior treatment regimens: Sub-analysis of the CheckMate 032 study – Ott P, et al

Conclusions

- **Nivolumab monotherapy demonstrated favourable clinical activity in this subset of heavily pretreated patients with advanced gastric/GEJ cancer, regardless of PD-L1 status**
- **OS after one year was 44.3% with durable responses in some patients**
- **Results were similar to those observed in the phase 3 ATTRACTION-2 study in Asian patients**

Ott P, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-007

O-016: Associations of quality of life (QoL) with adverse events and tumor response in patients with advanced gastric cancer: Exploratory analyses from RAINBOW and REGARD – Chau I, et al

Study objective

- To explore changes in QoL relative to treatment-emergent AEs and response in patients who participated in two phase 3 trials (RAINBOW and REGARD)

Methods

- QLQ-C30 v3.0 was completed at baseline and every 6 weeks
- Data was pooled for all treatment arms (n=1020)
- Logistic regression adjusted for baseline covariates was used to estimate ORs for selected treatment-emergent AEs occurrence (yes or no) and BOR groups (response, SD or other)
  - OR ≤0.85 with $p<0.05$ was considered meaningful
- ANOVA was used to compare changes from baseline in QoL scores based on occurrence of selected (by incidence and clinical symptoms) treatment-emergent AEs and BOR
  - p-value <0.05 considered significant

Developed based on abstract only

Chau I, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-016

O-016: Associations of quality of life (QoL) with adverse events and tumor response in patients with advanced gastric cancer: Exploratory analyses from RAINBOW and REGARD – Chau I, et al

Key results

- Multiple treatment-emergent AEs and BOR could be predicted by worsening QoL
- Changes in patient-reported insomnia and constipation did not predict any outcomes
- Significant differences in changes in QoL scales were also associated with multiple treatment-emergent AEs and BOR

Developed based on abstract only

Chau I, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-016

O-016: Associations of quality of life (QoL) with adverse events and tumor response in patients with advanced gastric cancer: Exploratory analyses from RAINBOW and REGARD – Chau I, et al

Key results (cont.)

Worsening in QoL scale	Prediction with OR ≤0.85 and p<0.05 based on logistic regression (QoL score change)	Outcomes with different changes in QoL based on ANOVA, p<0.05
Global QoL	Pyrexia (5 points) Worse BOR (10 points)	BOR
Physical functioning	Decreased appetite (10 points) Worse BOR (15 points)	Alopecia Neuropathy BOR
Role functioning	Decreased appetite (15 points) Fatigue (20 points) Nausea (15 points) Diarrhoea (10 points) Worse BOR (15 points)	Neuropathy BOR
Emotional functioning	Decreased appetite (10 points) Nausea (10 points) Worse BOR (15 points)	Decreased appetite Neuropathy BOR
Cognitive functioning	Decreased appetite (10 points)	Neutropenia (grade ≥3) BOR
Social functioning	Worse BOR (20 points)	Neuropathy BOR
Fatigue	Decreased appetite (10 points) Fatigue (15 points) Worse BOR (15 points)	Decreased appetite Neuropathy BOR
Nausea/vomiting	Nausea (10 points) Vomiting (10 points) Worse BOR (15 points)	Neuropathy BOR
Pain	Worse BOR (20 points)	Fatigue Vomiting Abdominal pain BOR
Dyspnoea	Anaemia (15 points)	Anaemia Abdominal pain BOR
Appetite loss	Decreased appetite (15 points) Fatigue (15 points) Worse BOR (20 points)	Decreased appetite Neuropathy BOR
Diarrhoea	Diarrhoea (5 points)	Anaemia Diarrhoea

Developed based on abstract only

Chau I, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-016

O-016: Associations of quality of life (QoL) with adverse events and tumor response in patients with advanced gastric cancer: Exploratory analyses from RAINBOW and REGARD – Chau I, et al

Conclusions

- **Changes in QoL scales/items were associated with changes in clinical status**
  - **10–20 point changes associated with BOR**
  - **10–15 point changes associated with AEs**
- **The most consistent changes in QoL were for BOR and investigator-reported appetite loss**

Developed based on abstract only

Chau I, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-016

CANCERS OF THE PANCREAS, SMALL BOWEL AND HEPATOBILIARY TRACT

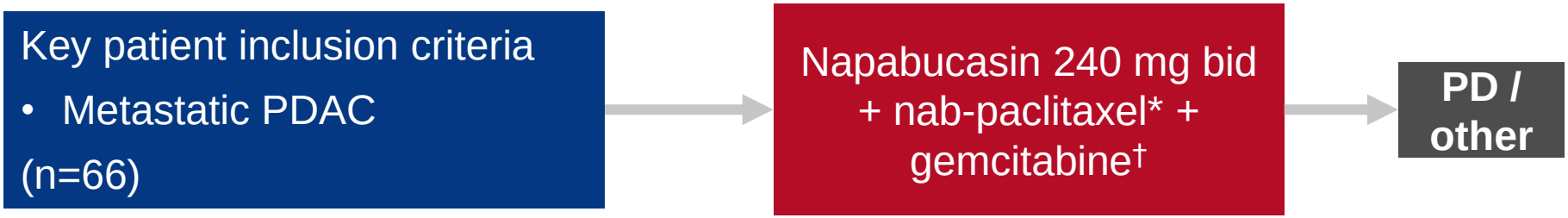
Cancers of the pancreas, small bowel and hepatobiliary tract

PANCREATIC CANCER

LBA-002: A phase 1b/II study of cancer stemness inhibitor napabucasin in combination with gemcitabine (gem) & nab-paclitaxel (nabptx) in metastatic pancreatic adenocarcinoma (mpdac) patients (pts) – Bekaii-Saab T

Study objective

- To assess the efficacy and safety of napabucasin in combination with nab-paclitaxel + gemcitabine in patients with metastatic PDAC



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- PFS, ORR, DCR, QoL, safety
- RP2D, PK

*Nab-paclitaxel 125 mg/m^2 q1w for 3 of every 4 weeks;
†gemcitabine 1000 mg/m^2 q1w for 3 of every 4 weeks

Developed based on abstract only

Bekaii-Saab T, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-002

LBA-002: A phase 1b/II study of cancer stemness inhibitor napabucasin in combination with gemcitabine (gem) & nab-paclitaxel (nabptx) in metastatic pancreatic adenocarcinoma (mpdac) patients (pts) – Bekaii-Saab T

Key results

- No significant PK interactions, dose-limiting or unexpected toxicities were reported
- Most common AEs:
  - Grade 1 diarrhoea, nausea, fatigue, neuropathy; grade 2 alopecia; grade 3 neutropenia

	DCR, n/N (%)		ORR, n/N (%)		1-year OS rate, %
	Evaluable	ITT	Evaluable	ITT	
All patients	51/55 (93)	51/66 (77)	30/60 (50)	30/71 (42)	NA
Enrolled ≥1 year ago	28/30 (93)	28/37 (76)	16/30 (53)	16/37 (43)	48
Enrolled ≥1 year ago + prescribed for ≥8 weeks	25/27 (93)		16/27 (59)		56

Conclusions

- **The data indicate that napabucasin may be combined with nab-paclitaxel + gemcitabine in patients with metastatic PDAC**
- **A phase 3 trial is ongoing to confirm the promising signs of efficacy in this setting**

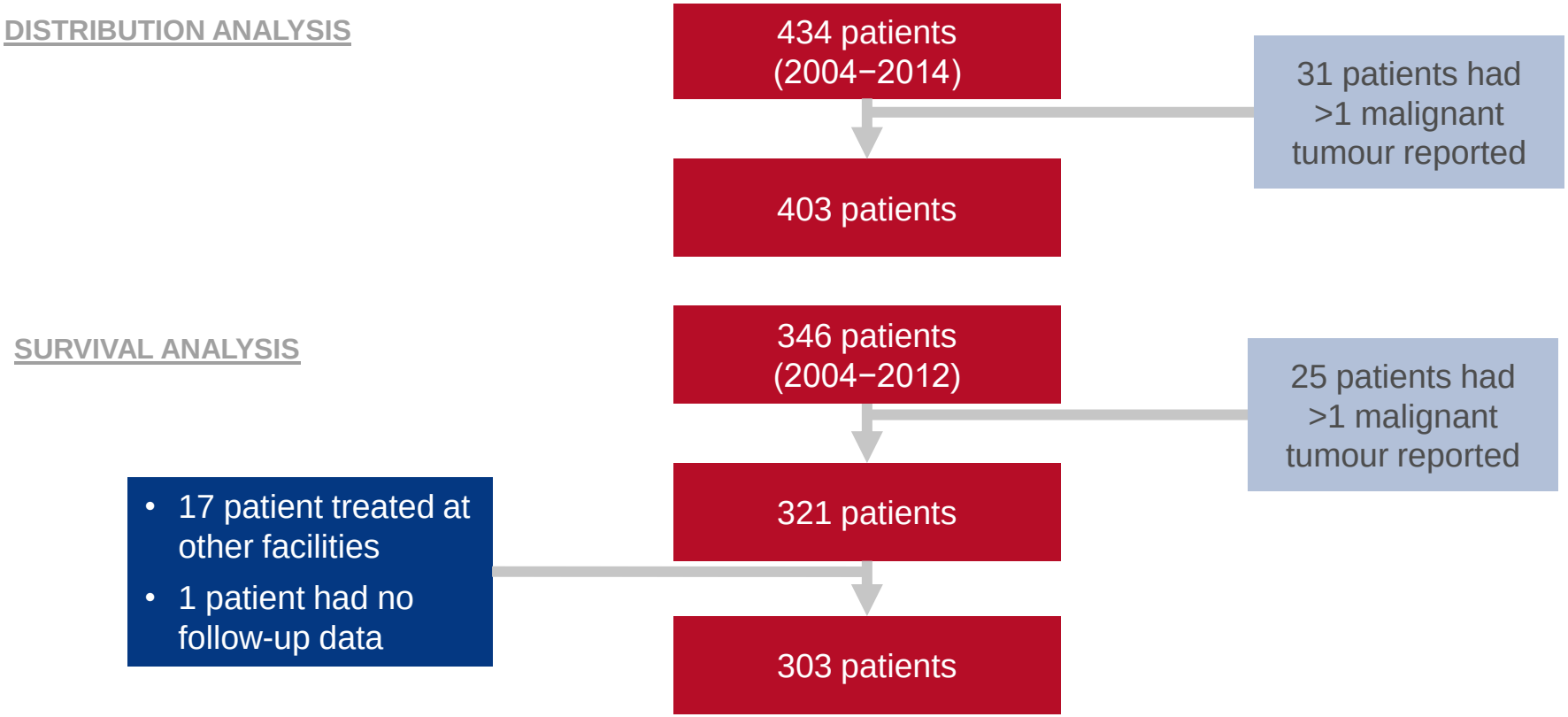
Developed based on abstract only

Bekaii-Saab T, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-002

O-002: Survival analysis of patients with solid pseudopapillary tumors of the pancreas in a multicenter retrospective cohort – Huffman B, et al

Study objective

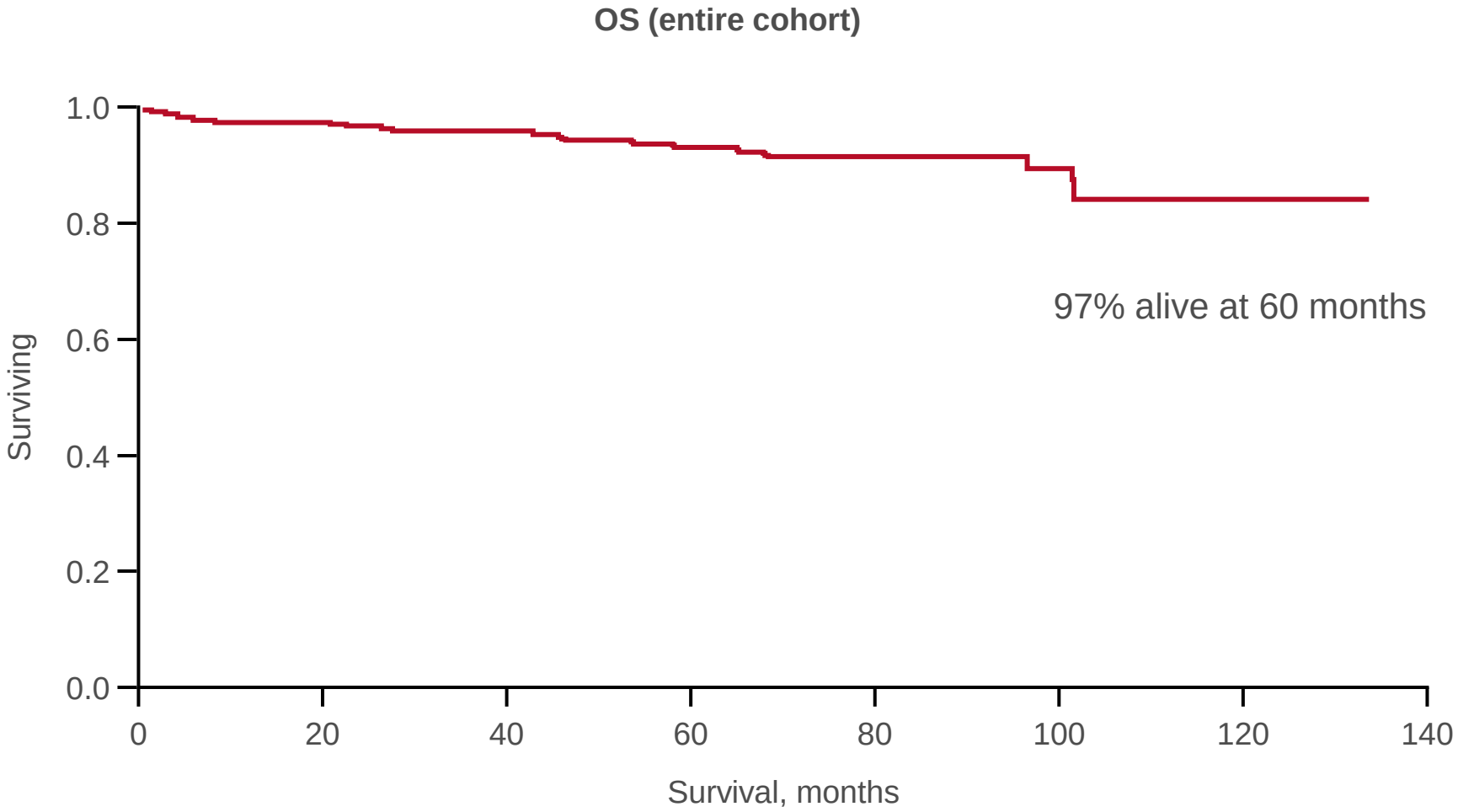
- To evaluate outcomes in patients diagnosed with pseudopapillary tumours of the pancreas between 2004 and 2014 using data collected in the National Cancer Data Base from US and Puerto Rican institutions



Huffman B, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-002

O-002: Survival analysis of patients with solid pseudopapillary tumors of the pancreas in a multicenter retrospective cohort – Huffman B, et al

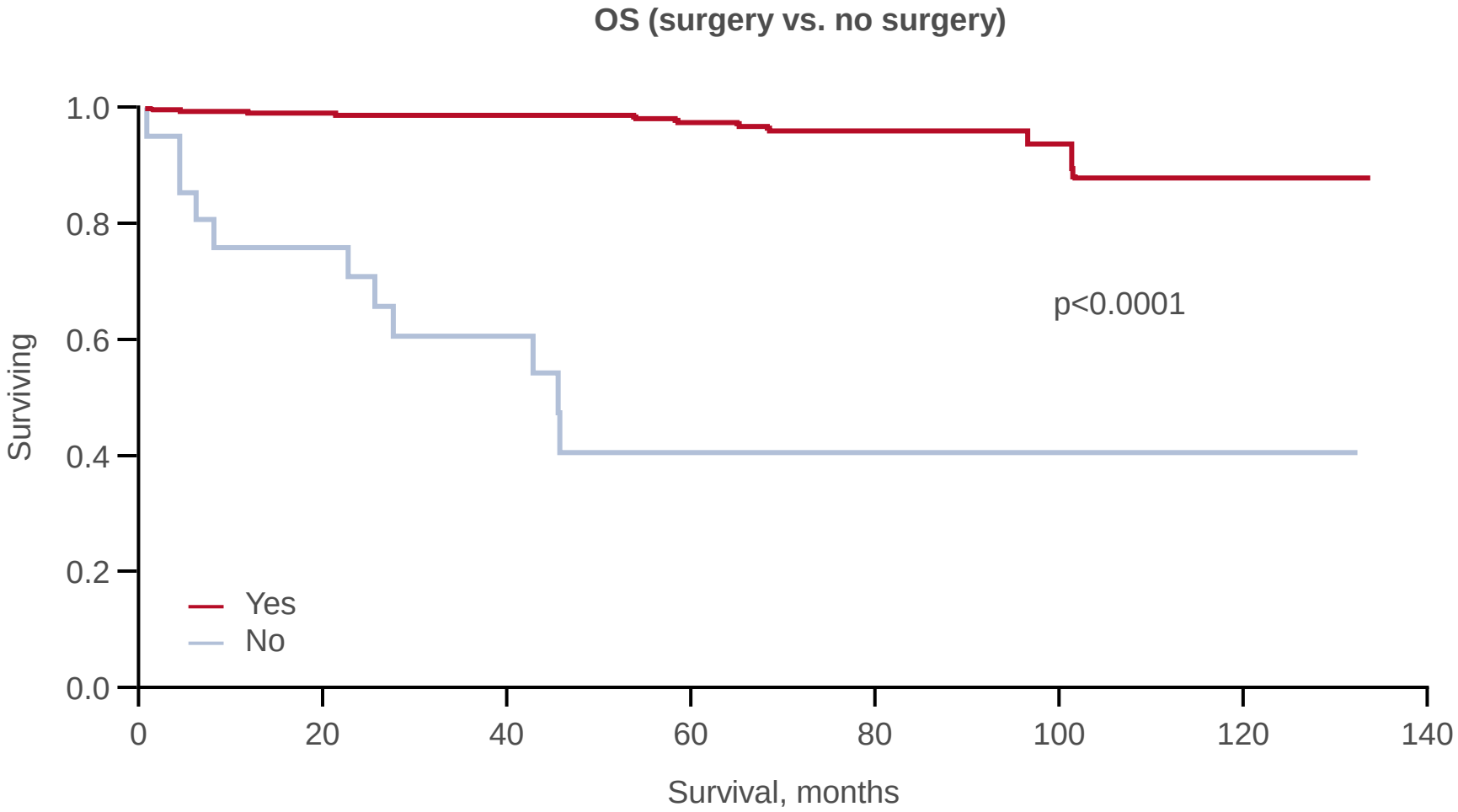
Key results



Huffman B, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-002

O-002: Survival analysis of patients with solid pseudopapillary tumors of the pancreas in a multicenter retrospective cohort – Huffman B, et al

Key results (cont.)



Huffman B, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-002

O-002: Survival analysis of patients with solid pseudopapillary tumors of the pancreas in a multicenter retrospective cohort – Huffman B, et al

Key results (cont.)

Patients, n (%)	n	Multivariate HR (95%CI)	p-value
Gender Male Female	 58 345	 0.299 (0.1, 0.8)	**0.0168**
Surgery No Yes	 31 368	 0.135 (0.04, 0.52)	**0.0041**
Presence of metastasis Yes No	 28 268	 0.269 (0.07, 0.9)	**0.0316**
Age	Continuous	1.19 (0.13, 9.5)	0.87

Huffman B, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-002

O-002: Survival analysis of patients with solid pseudopapillary tumors of the pancreas in a multicenter retrospective cohort – Huffman B, et al

Conclusions

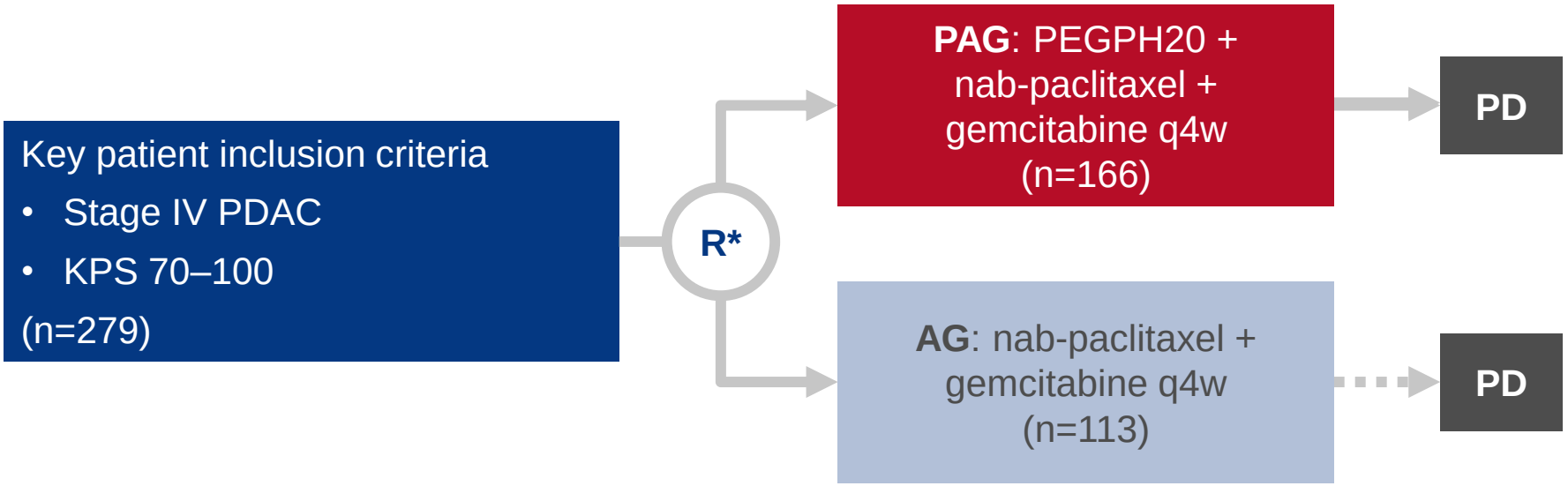
- **Survival was excellent after primary tumour resection in patients presenting with localised solid pseudopapillary tumours of the pancreas (98% at 5 years)**
- **According to multivariate analysis, female gender, surgical intervention and the absence of distant metastases were associated with improved survival**
- **Surgery led to better survival even in patients with metastatic stage IV disease with OS of 45 months**
- **All resectable patients should be considered for surgery**

Huffman B, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-002

O-003: PEGPH20 improves PFS in patients with metastatic pancreatic ductal adenocarcinoma: A randomized phase 2 study in combination with nab-paclitaxel/gemcitabine – Sunil H, et al

Study objective

- To evaluate the efficacy and rate of TE events in patients with untreated metastatic PDAC treated with PAG or AG



CO-PRIMARY ENDPOINTS

- PFS, TE event rate

SECONDARY ENDPOINTS

- PFS by HA level, ORR, OS

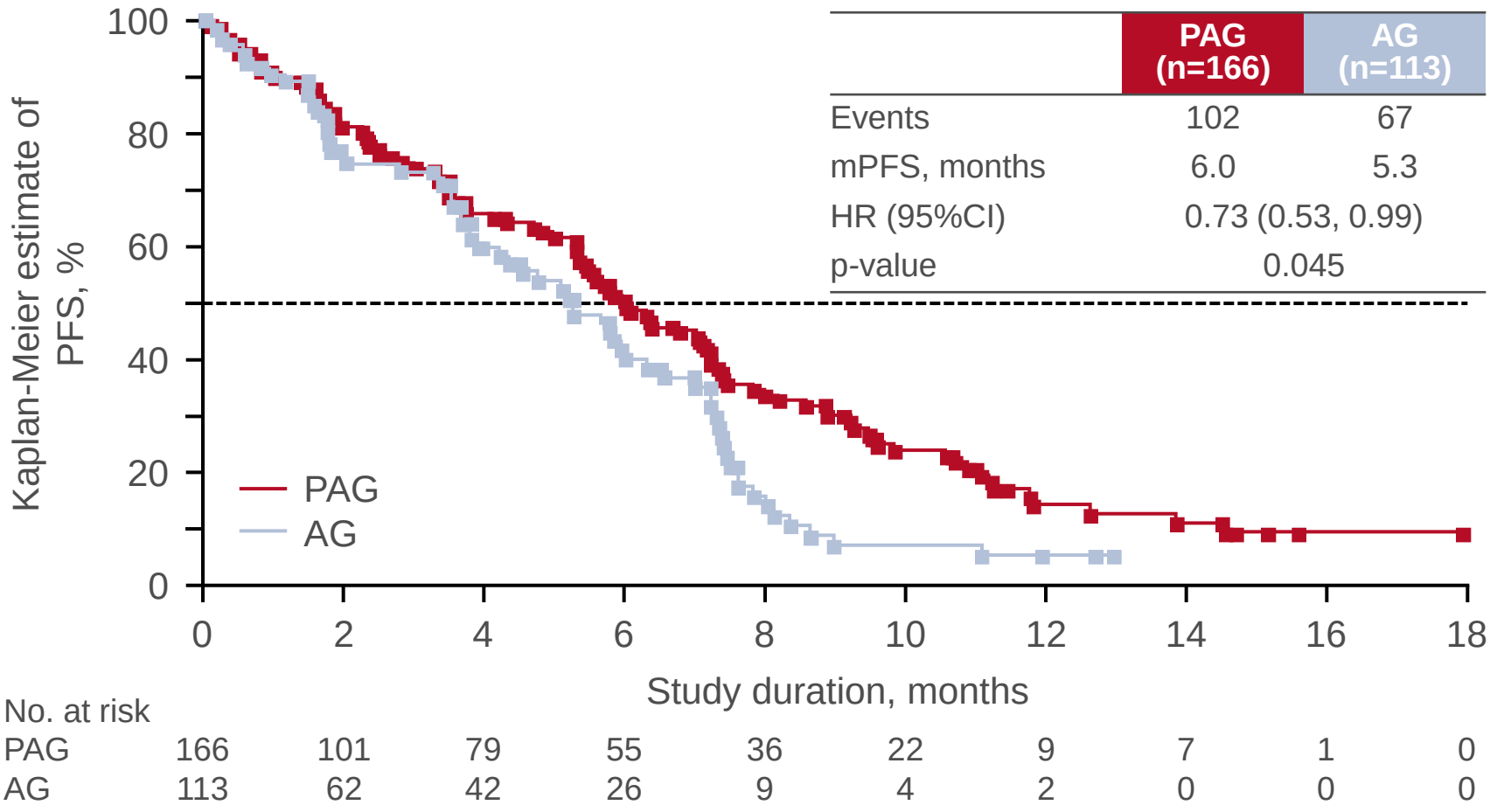
*1:1 in stage 1; 2:1 in stage 2 where patients at high risk of TE events had been excluded after the study was on hold

Sunil H, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-003

O-003: PEGPH20 improves PFS in patients with metastatic pancreatic ductal adenocarcinoma: A randomized phase 2 study in combination with nab-paclitaxel/gemcitabine – Sunil H, et al

Key results

PFS (combined stages 1 and 2)



	PAG (n=166)	AG (n=113)
Events	102	67
mPFS, months	6.0	5.3
HR (95%CI)	0.73 (0.53, 0.99)	
p-value	0.045	

No. at risk

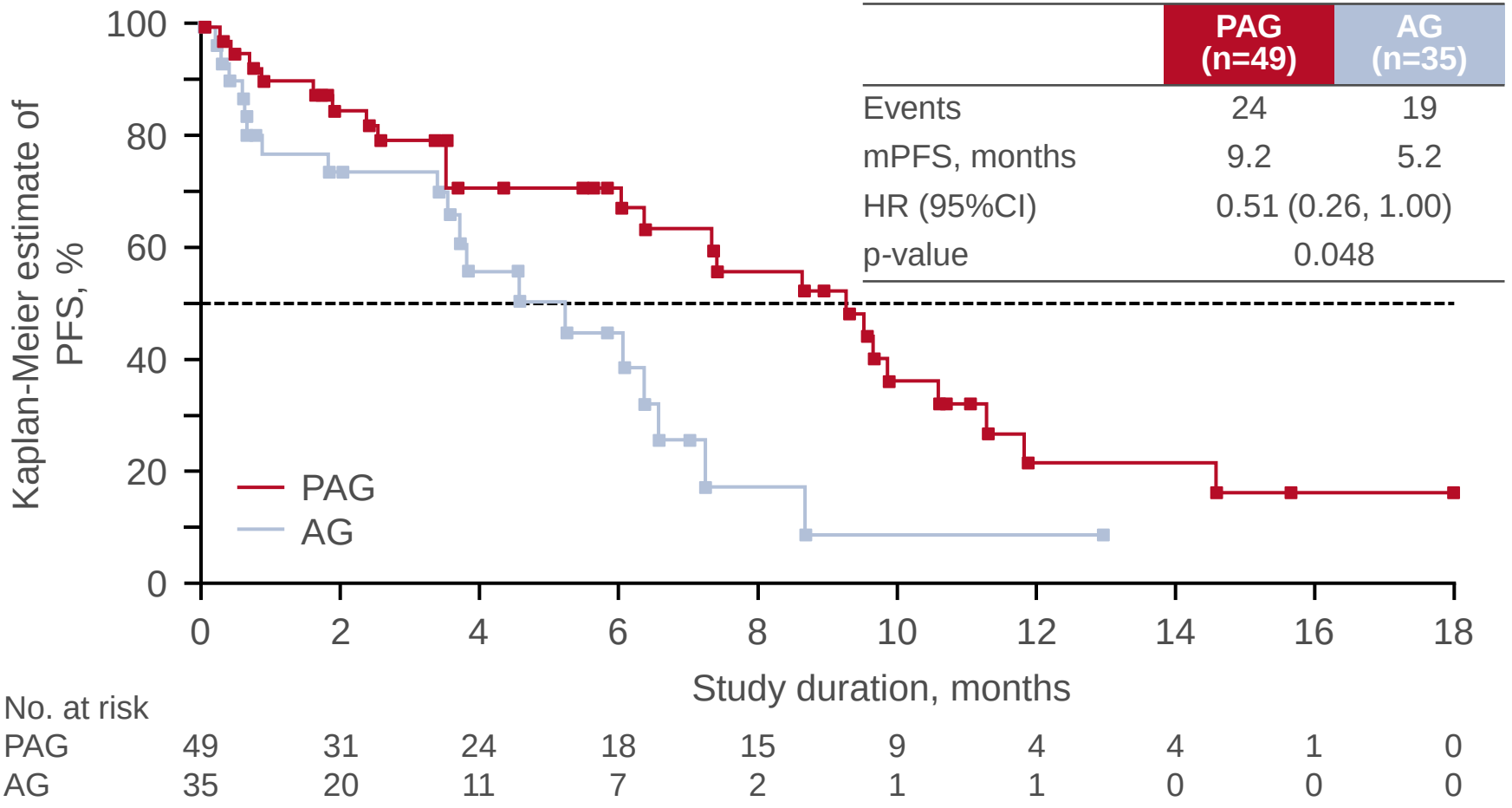
PAG	166	101	79	55	36	22	9	7	1	0
AG	113	62	42	26	9	4	2	0	0	0

Sunil H, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-003

O-003: PEGPH20 improves PFS in patients with metastatic pancreatic ductal adenocarcinoma: A randomized phase 2 study in combination with nab-paclitaxel/gemcitabine – Sunil H, et al

Key results (cont.)

PFS in HA-high population (combined stages 1 and 2)



	PAG (n=49)	AG (n=35)
Events	24	19
mPFS, months	9.2	5.2
HR (95%CI)	0.51 (0.26, 1.00)	
p-value	0.048	

No. at risk										
PAG	49	31	24	18	15	9	4	4	1	0
AG	35	20	11	7	2	1	1	0	0	0

Sunil H, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-003

O-003: PEGPH20 improves PFS in patients with metastatic pancreatic ductal adenocarcinoma: A randomized phase 2 study in combination with nab-paclitaxel/gemcitabine – Sunil H, et al

Key results (cont.)

	Enoxaparin prophylaxis dose	TE rate, n/N (%)	
		PAG	AG
Stage 1	NA	32/74 (43)	15/61 (25)
Stage 2*	40 mg/day	5/18 (28)	2/7 (29)
	1 mg/kg/day	7/68 (10)	2/32 (6)

- No difference in TE event rate observed by tumour HA level
- No difference in bleeding events by treatment arm

*TE rates for all stage 2 patients are 12/86 (14%) in PAG arm and 4/39 (10%) in AG arm

Sunil H, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-003

O-003: PEGPH20 improves PFS in patients with metastatic pancreatic ductal adenocarcinoma: A randomized phase 2 study in combination with nab-paclitaxel/gemcitabine – Sunil H, et al

Conclusions

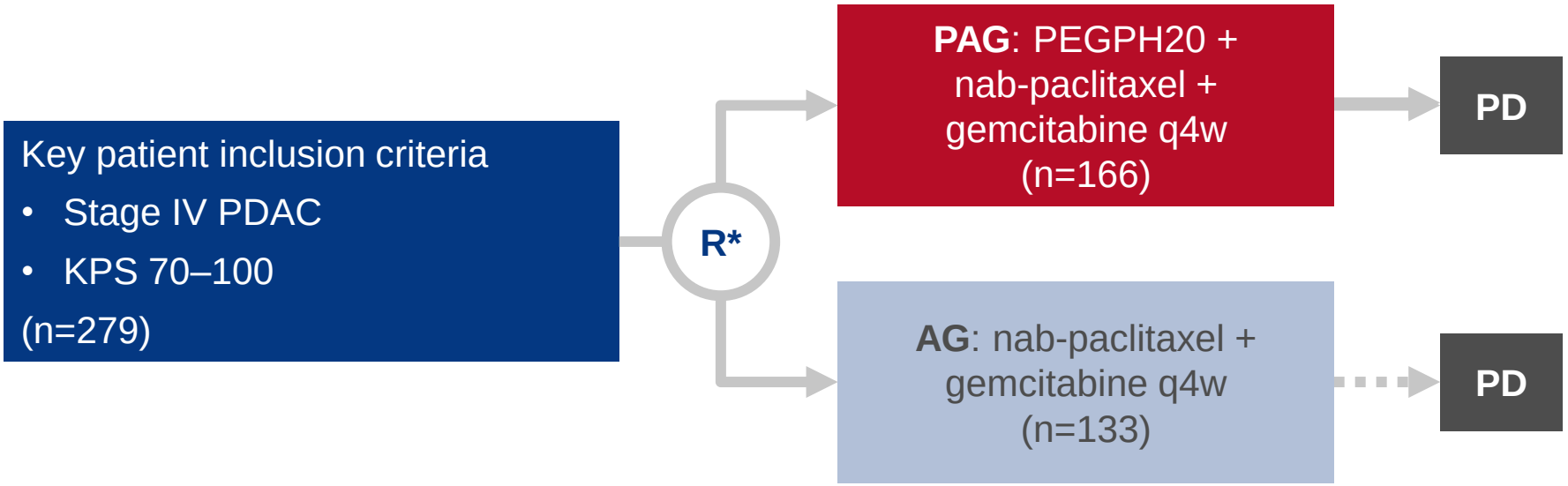
- **Addition of PEGPH20 improved PFS over nab-paclitaxel + gemcitabine alone**
- **Greatest improvement in PFS was observed in patients with high HA**
- **Protocol amendment in stage 2 to include screening for TE risk and thromboprophylaxis with enoxaparin eliminated the difference in TE rate between treatments**
- **HA may be a predictive biomarker to select patients for treatment with PEGPH20**
- **This is being investigated in an ongoing phase 3 study HALO-301**

Sunil H, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-003

O-028: Tumor hyaluronan may predict benefit from PEGPH20 when added to nab paclitaxel/gemcitabine in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDA) – Hendifar A, et al

Study objective

- To evaluate the efficacy and rate of TE events in patients with untreated metastatic PDAC treated with PAG or AG (analysis of stage 2 only)



CO-PRIMARY ENDPOINTS

- PFS, TE event rate

SECONDARY ENDPOINTS

- PFS by HA level, ORR, OS

*1:1 in stage 1; 2:1 in stage 2 where patients at high risk of TE events had been excluded after the study was on hold

Hendifar A, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-028

O-028: Tumor hyaluronan may predict benefit from PEGPH20 when added to nab paclitaxel/gemcitabine in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDA) – Hendifar A, et al

Key results

	Enoxaparin prophylaxis dose	PAG	AG
TE rate, n/N (%)	40 mg/day	5/18 (28)	2/7 (29)
	1 mg/kg/day	7/68 (10)	2/32 (6)

	AE severity	PAG	AG
Bleeding events, n/N (%)	All grade	31/86 (36)	14/39 (36)
	Grade 3/4	3/86 (4)	3/39 (8)

Hendifar A, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-028

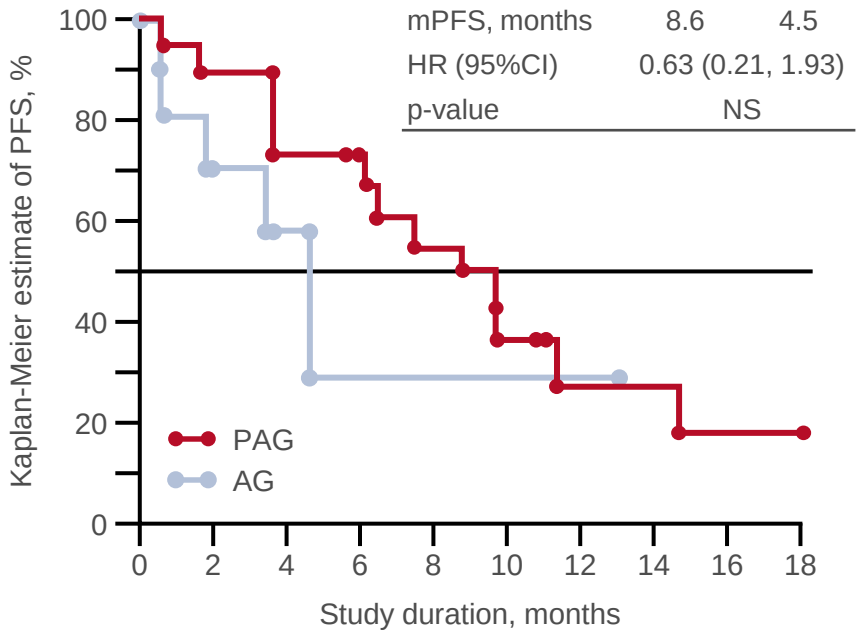
O-028: Tumor hyaluronan may predict benefit from PEGPH20 when added to nab paclitaxel/gemcitabine in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDA) – Hendifar A, et al

Key results (cont.)

PFS (stage 2)

HA-high

	PAG (n=25)	AG (n=12)
Events	13	5
mPFS, months	8.6	4.5
HR (95%CI)	0.63 (0.21, 1.93)	
p-value	NS	

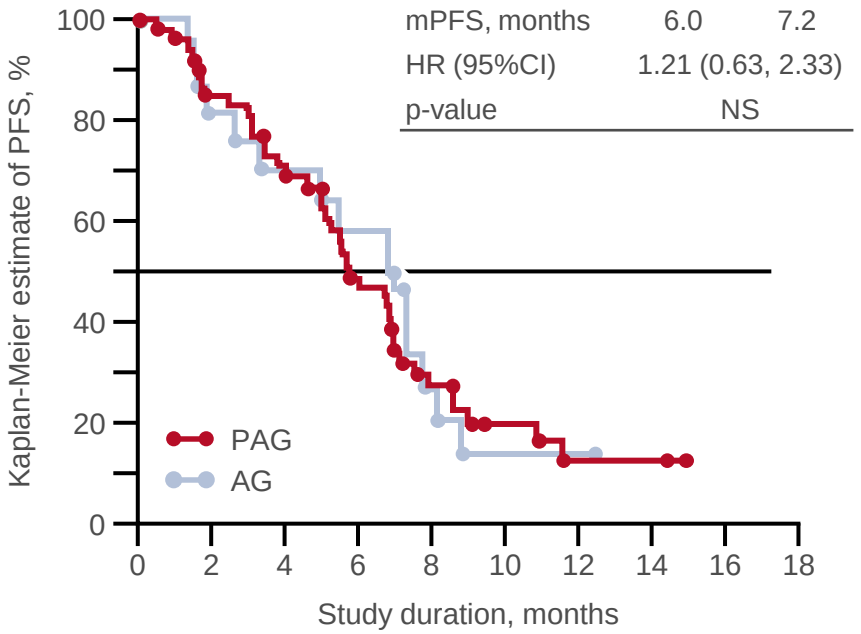


No. at risk

PAG	25	17	14	11	9	6	3	3	1	0
AG	12	6	3	1	1	1	1	0	0	0

HA-low

	PAG (n=55)	AG (n=25)
Events	40	15
mPFS, months	6.0	7.2
HR (95%CI)	1.21 (0.63, 2.33)	
p-value	NS	



No. at risk

PAG	55	40	33	24	12	6	3	3	1	0
AG	25	15	11	9	5	2	1	0	0	0

Hendifar A, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-028

O-028: Tumor hyaluronan may predict benefit from PEGPH20 when added to nab paclitaxel/gemcitabine in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDA) – Hendifar A, et al

Key results (cont.)

	PAG	AG	
HA-high	n=25 PFS 8.6 months **OS 11.7 months**	n=12 PFS 4.5 months **OS 7.8 months**	HR 0.63 **HR 0.52**
HA-low	n=55 PFS 6.0 months **OS 11.9 months**	n=25 PFS 7.2 months **OS 10.2 months**	HR 1.21 **HR 0.69**

Hendifar A, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-028

O-028: Tumor hyaluronan may predict benefit from PEGPH20 when added to nab paclitaxel/gemcitabine in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDA) – Hendifar A, et al

Conclusions

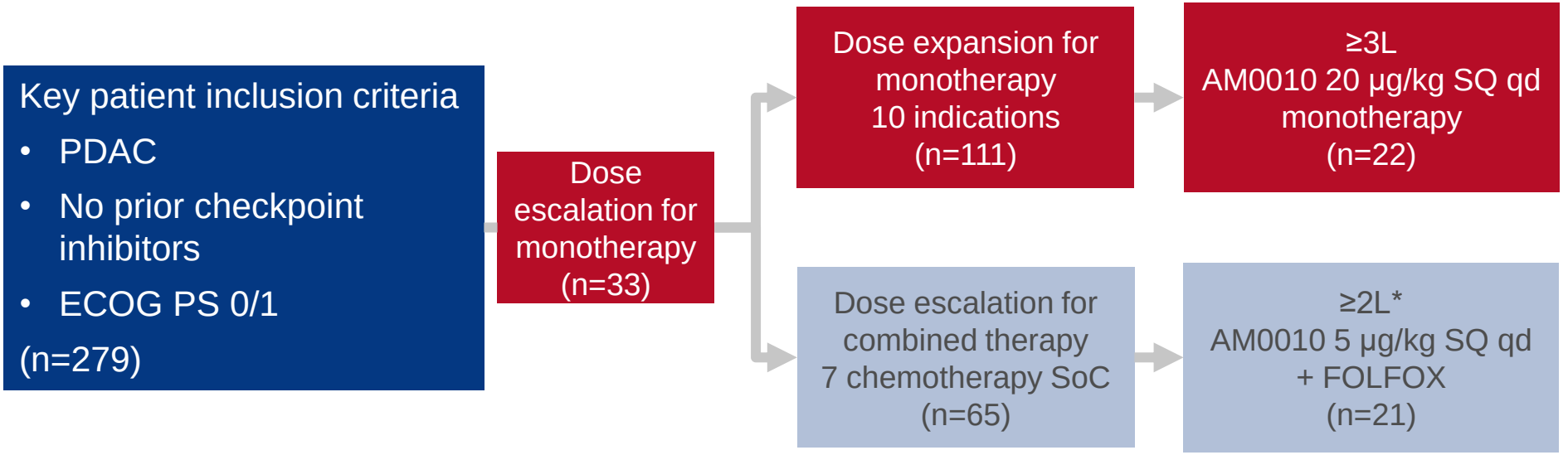
- **This is the first randomised study to use a molecularly targeted drug in PDAC**
- **Positive trends were observed for PFS and OS in patients with HA-high who were treated with PAG**
- **HA may be a predictive biomarker to select patients for treatment with PEGPH20 and may have prognostic value in metastatic PDAC**
- **This is being investigated in an ongoing phase 3 study HALO-301**

Hendifar A, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-028

O-004: Immunologic and objective tumor responses to PEGylated human IL-10 (AM0010) with 5-FU/LV and oxaliplatin (FOLFOX) in metastatic pancreatic adenocarcinoma (PDAC) – Hecht RJ, et al

Study objective

- Phase 1b study to investigate the safety and efficacy of AM0010 in combination with FOLFOX in at least 2L therapy of patients with metastatic PDAC



*Progressed on prior gemcitabine regime; no prior platin

Hecht RJ, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-004

O-004: Immunologic and objective tumor responses to PEGylated human IL-10 (AM0010) with 5-FU/LV and oxaliplatin (FOLFOX) in metastatic pancreatic adenocarcinoma (PDAC) – Hecht RJ, et al

Key results

- AM0010 + FOLFOX was generally well tolerated
- Grade 3/4 TRAEs included thrombocytopenia (52%) and anaemia (40%)
  - Majority were transient and reversible within 2–3 days of dose interruption
- A modified AM0010 dose schedule of 5 days on treatment followed by 2 days off treatment mitigated grade 3/4 thrombocytopenia and anaemia
  - Immune stimulation profile was retained

TRAEs (grade 3/4 occurring in ≥5%), n (%)	Grade 1/2		Grade 3/4	
	Monotherapy (n=22)	FOLFOX (n=25)	Monotherapy (n=22)	FOLFOX (n=25)
Blood and lymphatic system disorders				
Anaemia	7 (31.8)	5 (20.0)	3 (13.6)	10 (40.0)
Leukopenia	0	2 (8.0)	1 (4.5)	3 (12.0)
Neutropenia	0	3 (12.0)	0	9 (36.0)
Thrombocytopenia	6 (27.3)	5 (20.0)	7 (31.8)	13 (52.0)
General disorders and administration site conditions				
Fatigue	5 (22.7)	15 (60.0)	2 (9.1)	3 (12.0)
Pyrexia	4 (18.2)	3 (12.0)	0	0

Safety population included 4 patients in dose escalation and patients with prior FOLFIRINOX, prior platin

Hecht RJ, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-004

O-004: Immunologic and objective tumor responses to PEGylated human IL-10 (AM0010) with 5-FU/LV and oxaliplatin (FOLFOX) in metastatic pancreatic adenocarcinoma (PDAC) – Hecht RJ, et al

Key results (cont.)

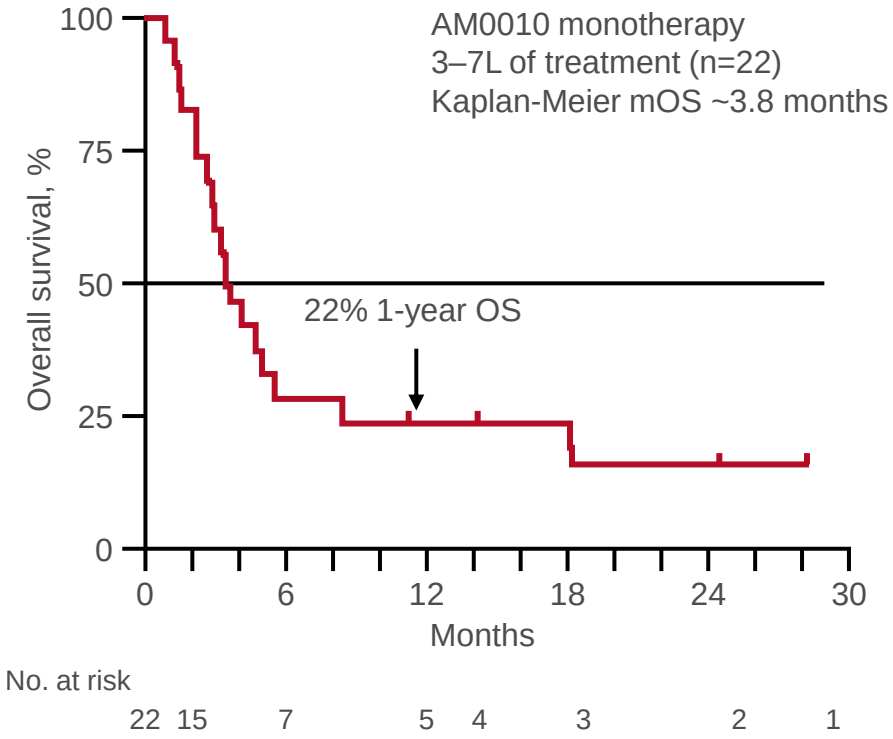
Treatment	Prior therapies, median (range)	DCR, n (%)	ORR, n (%)	CR, n (%)	mPFS, months	mOS, months
AM0010 (n=15/22)	3 (2−6)	8 (53)	0	0	1.7	3.8
AM0010 + FOLFOX (n=19/21)	2 (1−5) no prior platinum	15 (79)	3 (16)	2 (11)	3.5	10.2
FOLFOX (Zaanan et al. BMC 2014)	1	36%	0	0	1.7	4.3

Hecht RJ, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-004

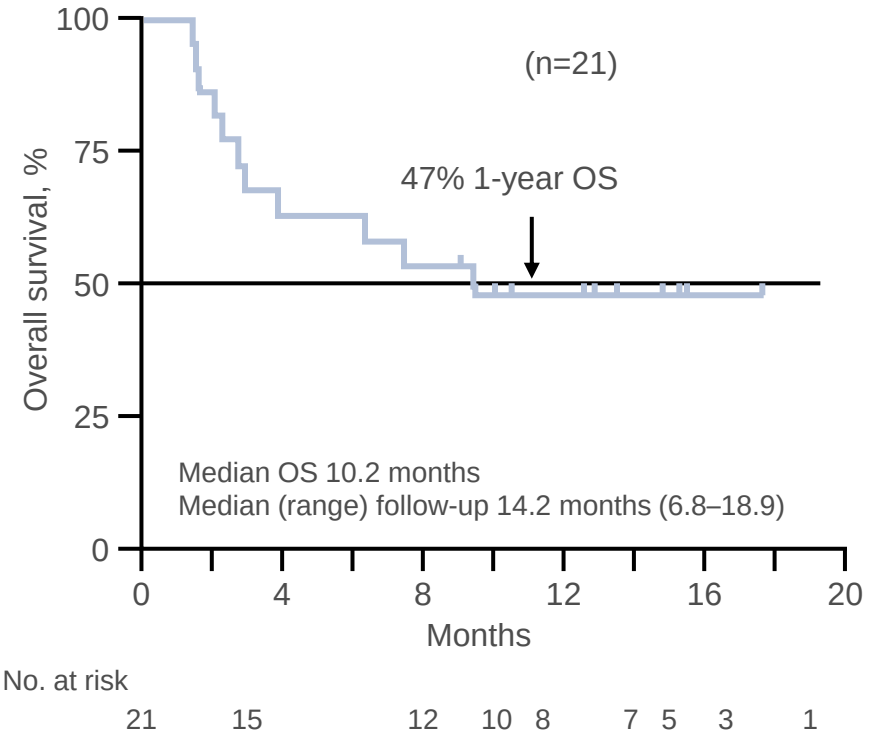
O-004: Immunologic and objective tumor responses to PEGylated human IL-10 (AM0010) with 5-FU/LV and oxaliplatin (FOLFOX) in metastatic pancreatic adenocarcinoma (PDAC) – Hecht RJ, et al

Key results (cont.)

OS (AM0010 monotherapy)



OS (AM0010 + FOLFOX)



Hecht RJ, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-004

O-004: Immunologic and objective tumor responses to PEGylated human IL-10 (AM0010) with 5-FU/LV and oxaliplatin (FOLFOX) in metastatic pancreatic adenocarcinoma (PDAC) – Hecht RJ, et al

Conclusions

- **AM0010 was well tolerated as monotherapy or in combination with FOLFOX**
- **Anaemia, thrombocytopenia, fatigue and fever were the most common TRAEs**
- **There were no autoimmune-related AEs during treatment**
- **Survival results appear to be promising**
- **Preliminary data suggests that immune activation is correlated with outcome**

Hecht RJ, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-004

Cancers of the pancreas, small bowel and hepatobiliary tract

BILIARY TRACT CANCER

O-020: Early clinical efficacy of TAS-120, a covalently bound FGFR inhibitor, in patients with cholangiocarcinoma – Goyal L, et al

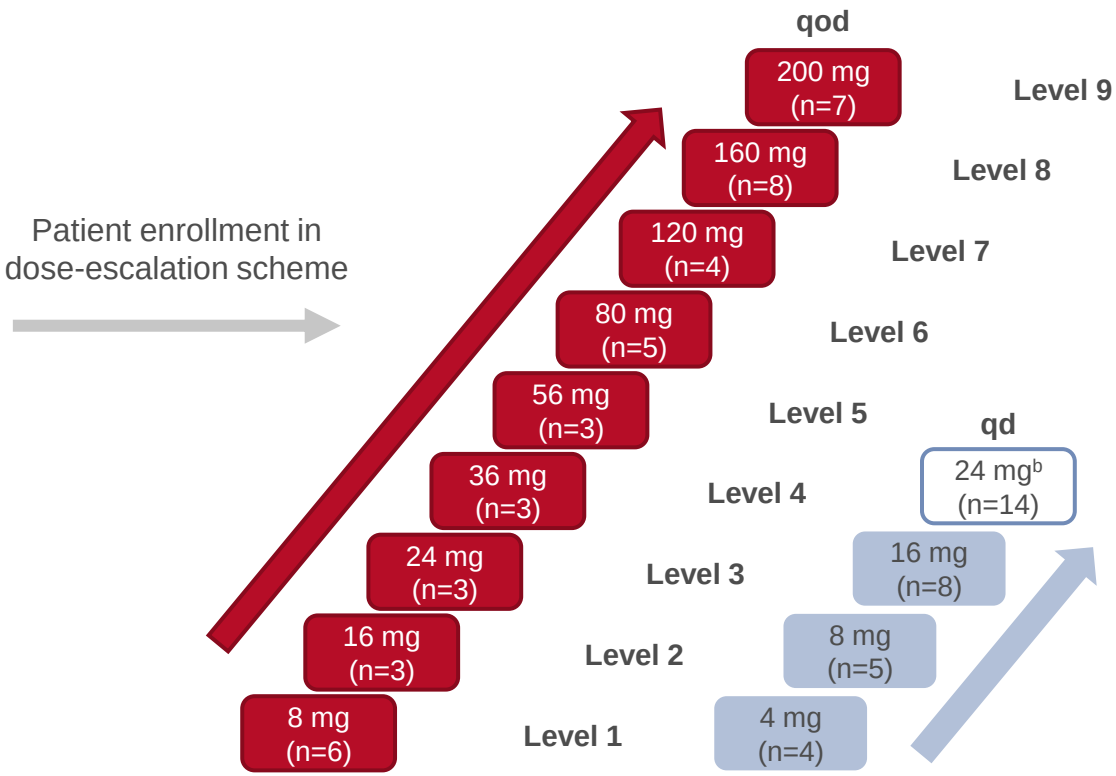
Study objective

- To investigate the efficacy of the covalently bound FGFR inhibitor, TAS-120, in patients with cholangiocarcinoma

Key patient inclusion criteria

- Locally confirmed FGF/FGFR alteration[a]
- Unresectable or metastatic disease
- Failed standard therapies
- ECOG PS 0/1

(n=19 in dose escalation; n=4 in dose expansion)



PRIMARY ENDPOINTS

- MTD, RP2D

SECONDARY ENDPOINTS

- Safety, preliminary anti-tumour activity

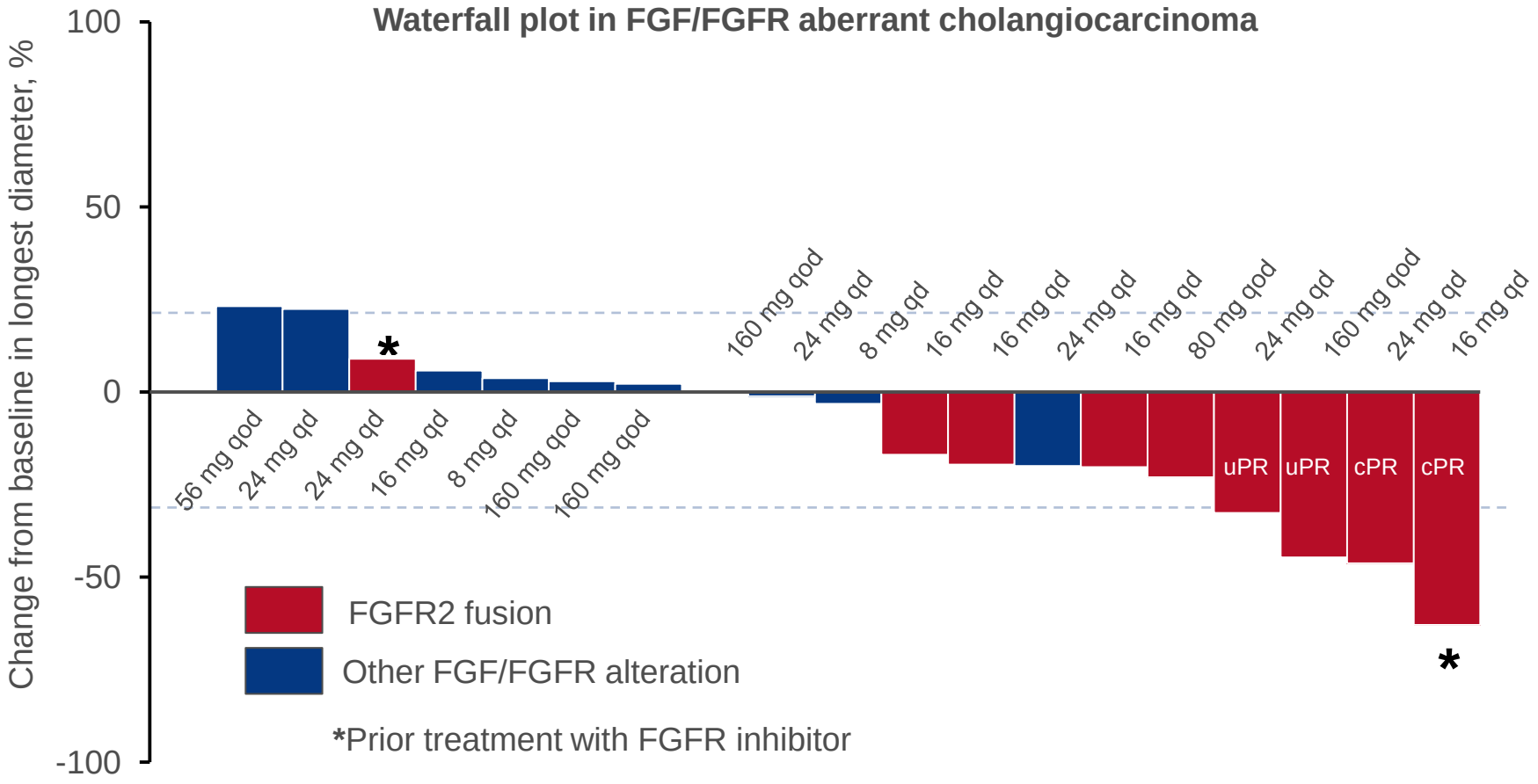
[a]From dose level 1 in qd and dose level 5 in qod

[b]24 mg qd is the DLT

Goyal L, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-020

O-020: Early clinical efficacy of TAS-120, a covalently bound FGFR inhibitor, in patients with cholangiocarcinoma – Goyal L, et al

Key results

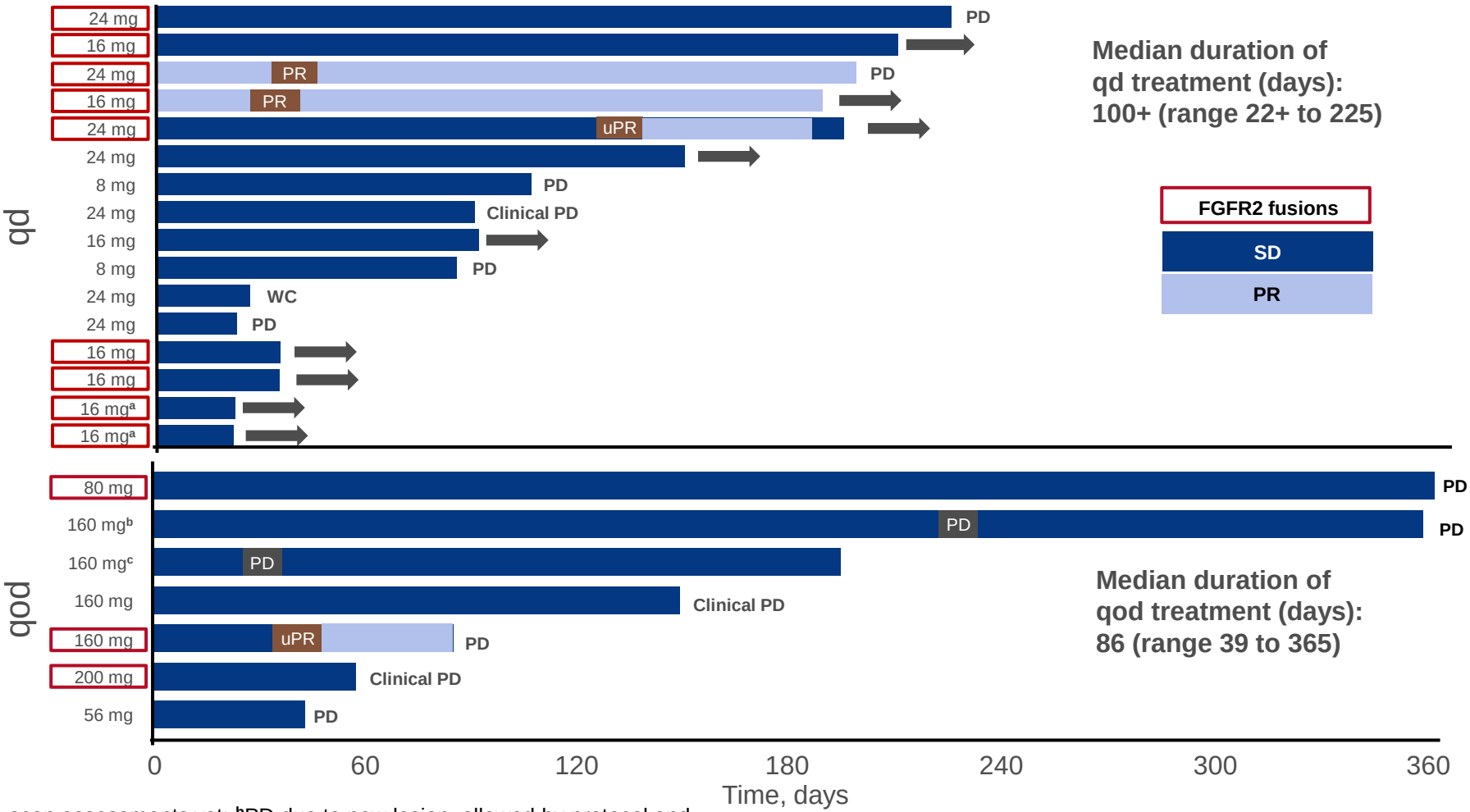


4 of the 23 patients are not included as they have no scans available yet; of these, 3 had prior FGFRi; Cut-off date: May 12, 2017

Goyal L, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-020

O-020: Early clinical efficacy of TAS-120, a covalently bound FGFR inhibitor, in patients with cholangiocarcinoma – Goyal L, et al

Key results (cont.)

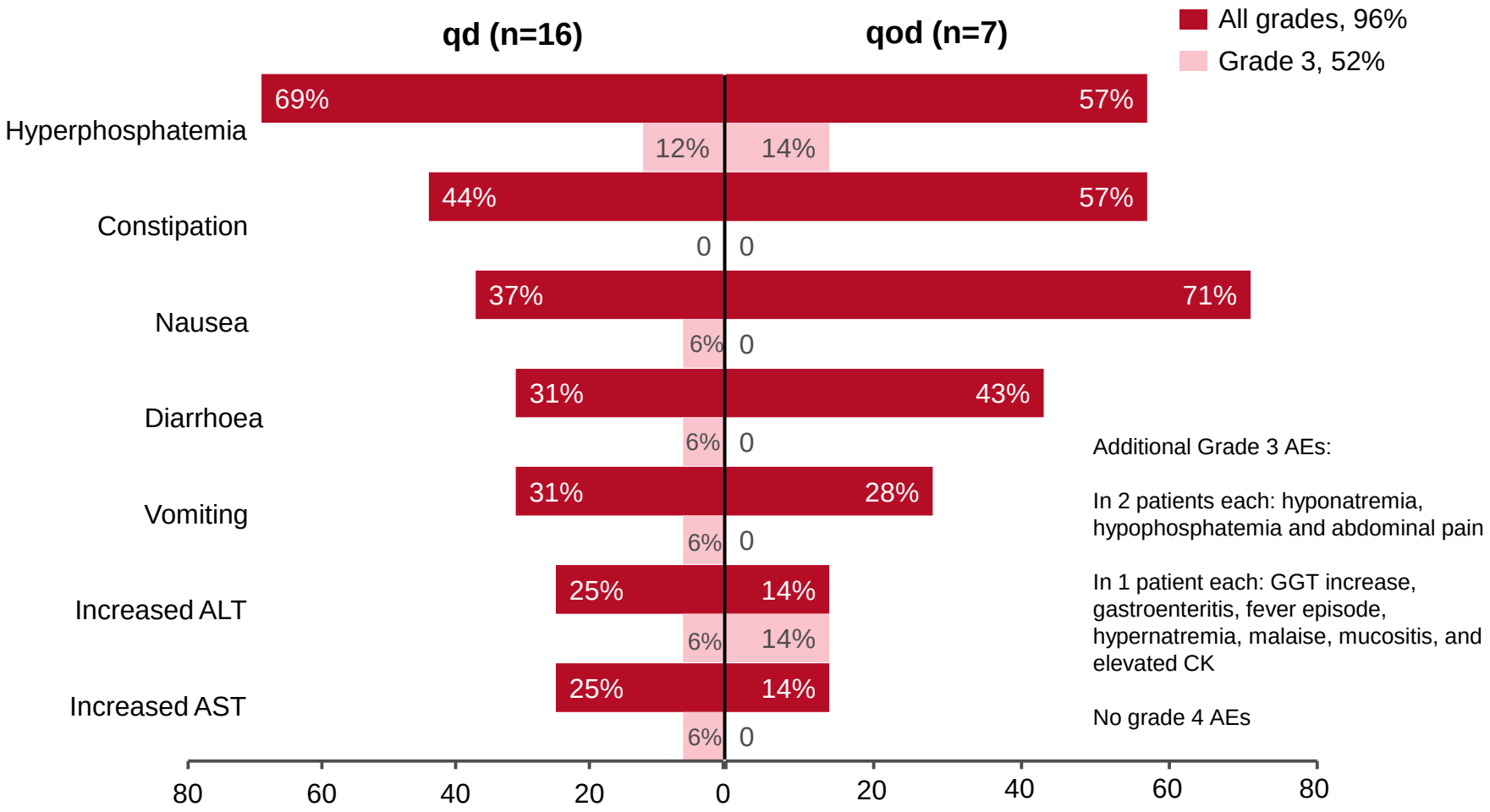


[a]No scan assessments yet; [b]PD due to new lesion, allowed by protocol and physician decision to continue study; [c]PD based on non-target lesions, physician decision to continue the study and patient is ongoing

Goyal L, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-020

O-020: Early clinical efficacy of TAS-120, a covalently bound FGFR inhibitor, in patients with cholangiocarcinoma – Goyal L, et al

Key results (cont.)



Additional Grade 3 AEs:

In 2 patients each: hyponatremia, hypophosphatemia and abdominal pain

In 1 patient each: GGT increase, gastroenteritis, fever episode, hypernatremia, malaise, mucositis, and elevated CK

No grade 4 AEs

Goyal L, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-020

O-020: Early clinical efficacy of TAS-120, a covalently bound FGFR inhibitor, in patients with cholangiocarcinoma – Goyal L, et al

Conclusions

- **In patients with cholangiocarcinoma who have FGFR2 gene fusions TAS-120 demonstrated early clinical activity**
- **Efficacy was shown in patients who had progressed during previous treatment with FGFR inhibitors**
- **TAS-120 showed an acceptable toxicity profile**
- **Therefore, TAS-120 may be a treatment option among patients who progress on a prior reversible FGFR inhibitor**
- **Further clinical development of TAS-120 at qd dosing, including in cholangiocarcinoma patients, is in progress**

Goyal L, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-020

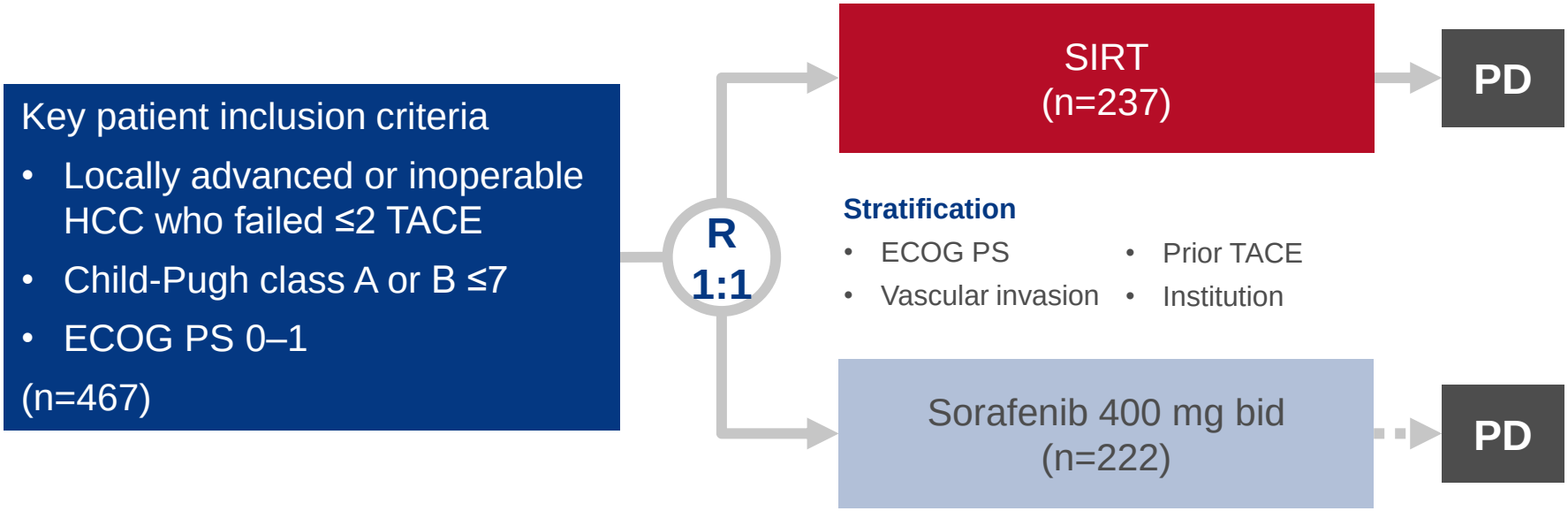
Cancers of the pancreas, small bowel and hepatobiliary tract

HEPATOCELLULAR CARCINOMA

LBA-001: Efficacy, tolerability and impact on quality of life of selective internal radiation therapy (with yttrium-90 resin microspheres) or sorafenib in patients with locally advanced hepatocellular carcinoma: The SARAH trial – Bouattour M, et al

Study objective

- To compare the efficacy and safety of SIRT using yttrium-90 resin microspheres with sorafenib in patients with intermediate and advanced HCC



PRIMARY ENDPOINT

- OS

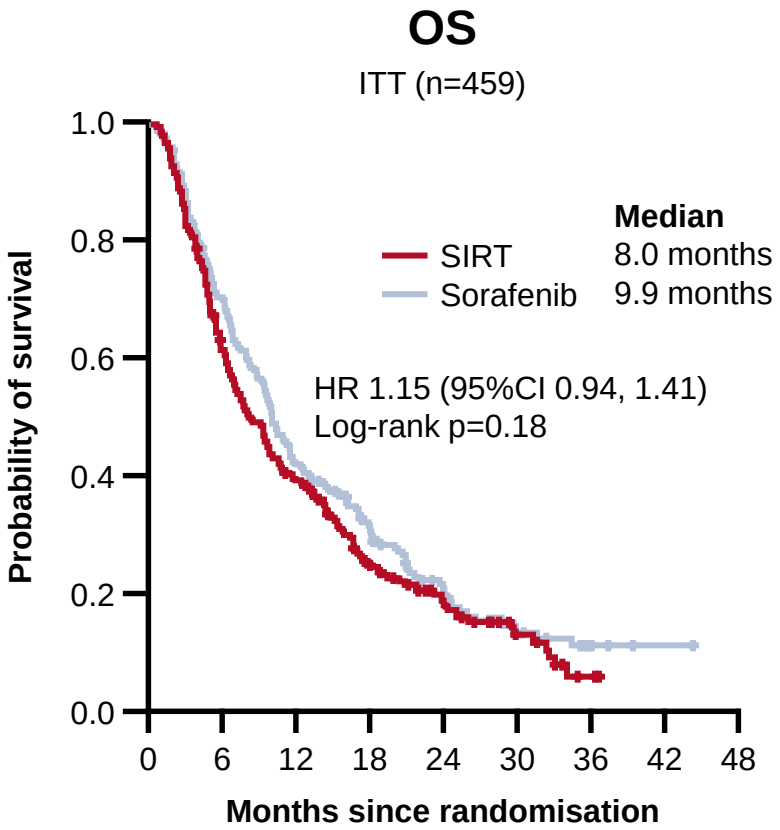
SECONDARY ENDPOINTS

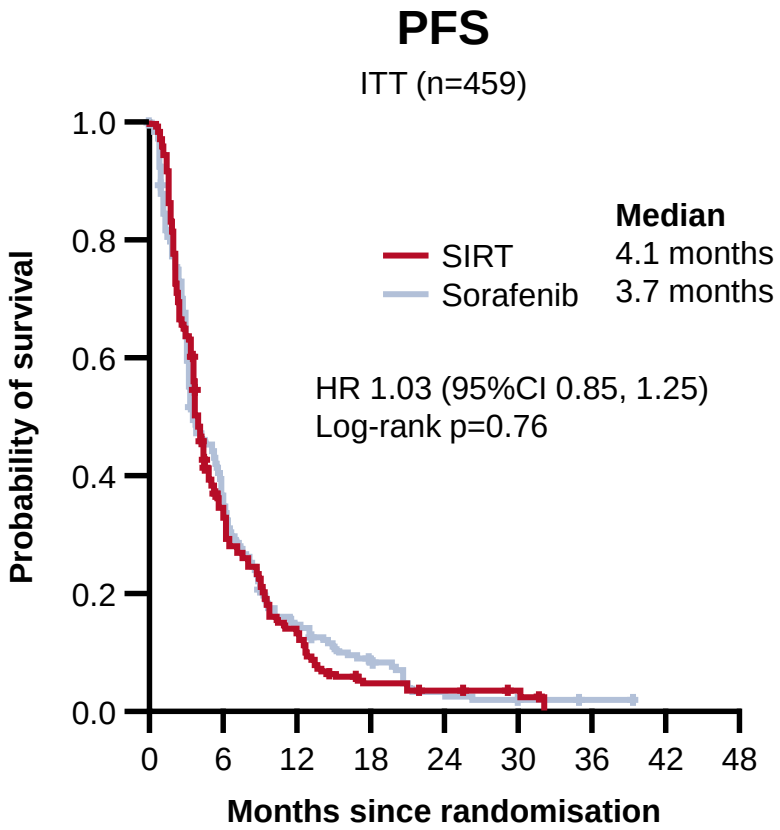
- PFS, time to radiologic progression, tumour response, safety, QoL

Bouattour M, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-001

LBA-001: Efficacy, tolerability and impact on quality of life of selective internal radiation therapy (with yttrium-90 resin microspheres) or sorafenib in patients with locally advanced hepatocellular carcinoma: The SARAH trial – Bouattour M, et al

Key results



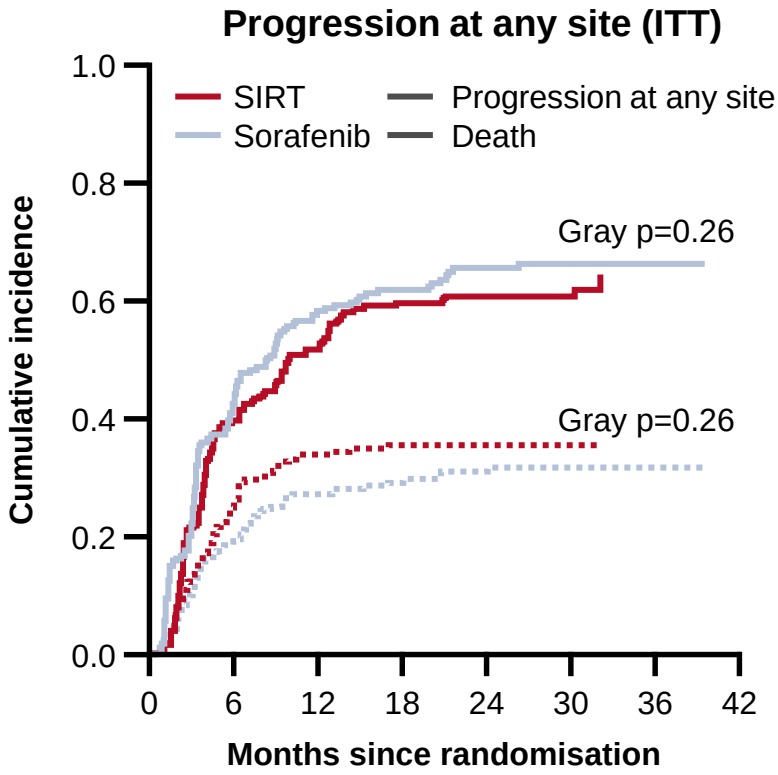


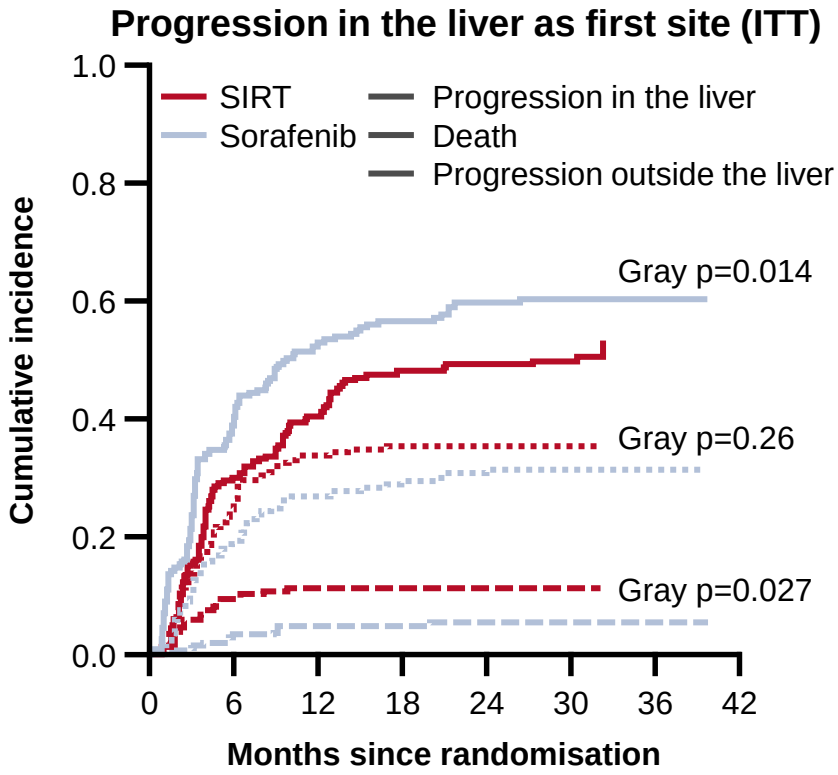
Bouattour M, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-001

LBA-001: Efficacy, tolerability and impact on quality of life of selective internal radiation therapy (with yttrium-90 resin microspheres) or sorafenib in patients with locally advanced hepatocellular carcinoma: The SARAH trial – Bouattour M, et al

Key results (cont.)

Radiologic progression





Tumour response (RECIST 1.1), n (%)	SIRT (n=190)	Sorafenib (n=198)	p-value
ORR (CR + PR)	36 (19.0)	23 (15.2)	0.042

Bouattour M, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-001

LBA-001: Efficacy, tolerability and impact on quality of life of selective internal radiation therapy (with yttrium-90 resin microspheres) or sorafenib in patients with locally advanced hepatocellular carcinoma: The SARAH trial – Bouattour M, et al

Key results (cont.)

TRAEs of interest in safety population, n (%)	SIRT (n=226)		Sorafenib (n=216)		p-value	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Fatigue	128 (41.6)	20 (8.8)	268 (64.8)	45 (19.0)	**<0.001**	**0.002**
Weight loss	16 (6.2)	0	63 (21.3)	6 (2.8)	**<0.001**	**0.013**
Hand-foot skin reaction	1 (0.4)	1 (0.4)	78 (20.8)	13 (5.6)	**<0.001**	**0.001**
Anorexia	34 (13.3)	7 (3.1)	132 (32.4)	11 (4.6)	**<0.001**	0.40
Diarrhoea	37 (12.8)	3 (1.3)	316 (67.6)	37 (13.9)	**<0.001**	**<0.001**
Nausea/vomiting	40 (11.5)	1 (0.4)	88 (23.1)	5 (2.3)	**0.001**	0.11
Abdominal pain	65 (20.4)	6 (2.7)	113 (29.2)	16 (6.5)	**0.032**	**0.05**
GI ulceration	7 (1.8)	5 (1.3)	1 (0.5)	1 (0.5)	0.37	0.62
GI bleeding	12 (4.0)	11 (4.0)	17 (6.5)	10 (3.7)	0.24	0.88
Ascites	39 (12.4)	15 (4.9)	31 (10.6)	11 (4.2)	0.57	0.72
Liver dysfunction	75 (17.3)	28 (9.3)	100 (21.8)	34 (12.5)	0.23	0.28
Radiation hepatitis	0	0	0	0	-	-
Hypertension	7 (2.7)	0	53 (13.0)	5 (2.3)	**<0.001**	**0.027**

Bouattour M, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-001

LBA-001: Efficacy, tolerability and impact on quality of life of selective internal radiation therapy (with yttrium-90 resin microspheres) or sorafenib in patients with locally advanced hepatocellular carcinoma: The SARAH trial – Bouattour M, et al

Key results (cont.)

- QoL* with SIRT vs. sorafenib (ITT, n=459)
  - Group effect: p=0.005, time effect: p<0.001
  - Group time interaction: p=0.045

Conclusions

- **OS was not improved for SIRT vs. sorafenib in patients with locally advanced or inoperable HCC who had failed after TACE**
- **SIRT was associated with improved tumour response, fewer TRAEs and a better QoL compared with sorafenib**
- **In the SIRT group, prognostic factors, cost effectiveness and dose-related efficacy will be further evaluated**

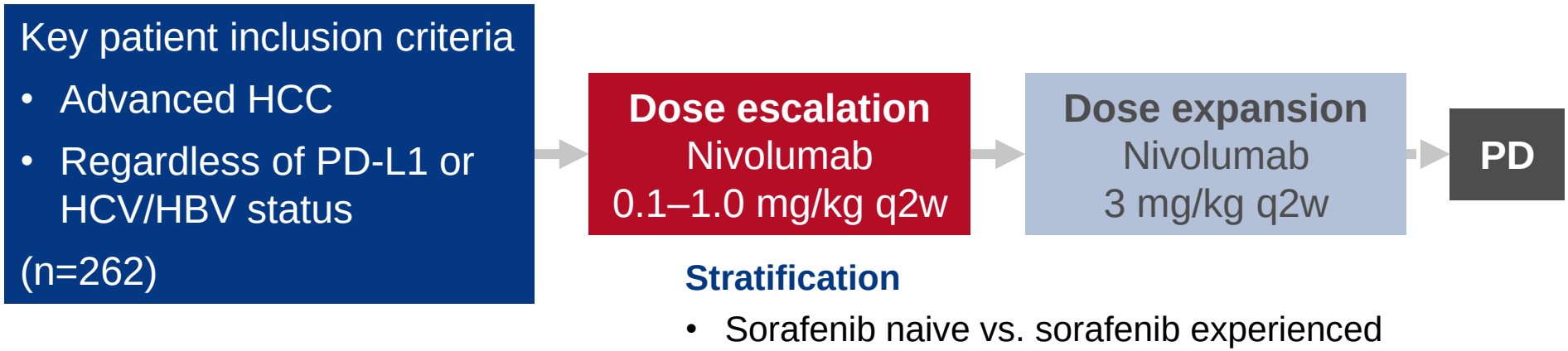
*Analysed using a linear mixed-effect model

Bouattour M, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-001

O-008: Efficacy and safety of nivolumab in patients with advanced hepatocellular carcinoma analyzed by patient age: A sub-analysis of the CheckMate 040 study – Melero I, et al

Study objective

- To evaluate the efficacy and safety of nivolumab according to age group in patients with advanced HCC



PRIMARY ENDPOINTS

- Safety (dose escalation)
- ORR (dose expansion)

Developed based on abstract only

Melero I, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-008

O-008: Efficacy and safety of nivolumab in patients with advanced hepatocellular carcinoma analyzed by patient age: A sub-analysis of the CheckMate 040 study – Melero I, et al

Key results

	<65 years (n=142)	65–<75 years (n=89)	≥65 years (n=120)	≥75 years (n=31)
ORR by blinded independent central review, n (%) [95%CI]	24 (16.9) [11.1, 24.1]	16 (18.0) [10.6, 27.5]	20 (16.7) [10.5, 24.6]	4 (12.9) [3.6, 29.8]
Sorafenib naïve, n/N (%)	8/38 (21.1)	8/30 (26.7)	8/42 (19.0)	0/12 (0)
Sorafenib experienced, n/N (%)	16/104 (15.4)	8/59 (13.6)	12/78 (15.4)	4/19 (21.1)
ORR by investigator assessment, n (%) [95%CI]	28 (19.7) [13.5, 27.2]	20 (22.5) [14.3, 32.6]	24 (20.0) [13.3, 28.3]	4 (12.9) [3.6, 29.8]
Sorafenib naïve, n/N (%)	8/38 (21.1)	10/30 (33.3)	10/42 (23.8)	0/12 (0)
Sorafenib experienced, n/N (%)	20/104 (19.2)	10/59 (16.9)	14/78 (17.9)	4/19 (21.1)

Conclusions

- **In patients with advanced HCC, it appeared that ORRs with nivolumab were not affected by age**
- **Across all age groups, the safety profile of nivolumab was manageable***

Developed based on abstract only

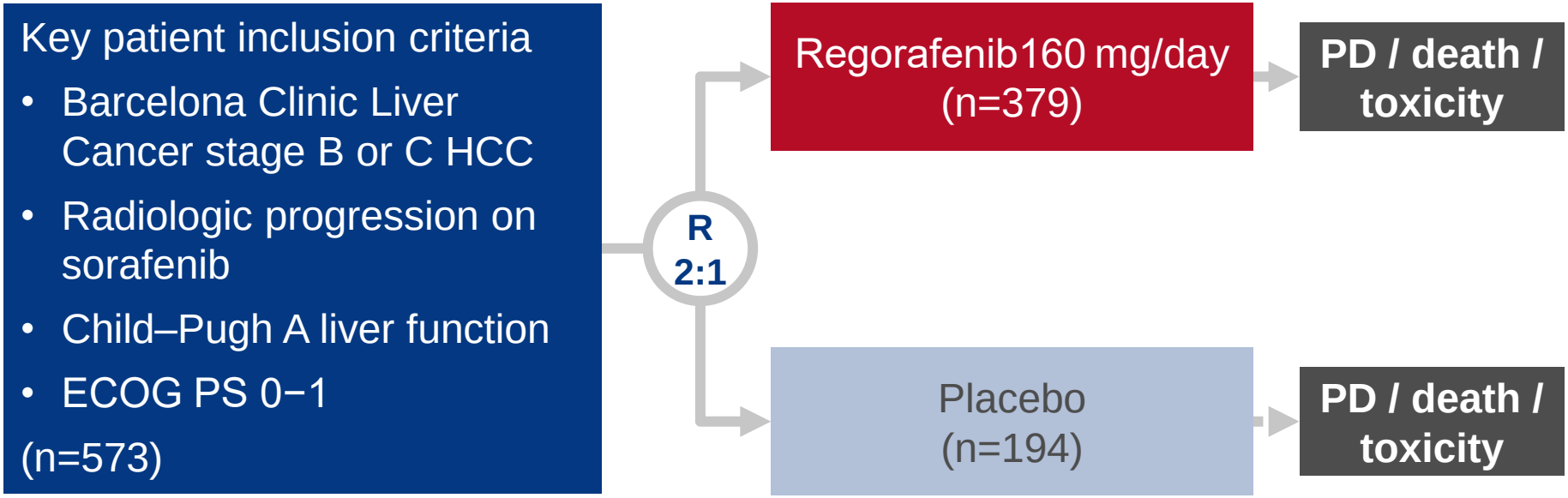
*Data not shown

Melero I, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-008

O-009: Updated overall survival (OS) analysis from the international, phase 3, randomized, placebo-controlled RESORCE trial of regorafenib for patients with hepatocellular carcinoma (HCC) who progressed on sorafenib treatment – Bruix J, et al

Study objective

- To report updated OS data from the RESORCE trial of regorafenib vs. placebo in patients with unresectable HCC who had progressed on sorafenib



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- PFS, TTP, DCR, ORR, safety

Developed based on abstract only

Bruix J, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-009

O-009: Updated overall survival (OS) analysis from the international, phase 3, randomized, placebo-controlled RESORCE trial of regorafenib for patients with hepatocellular carcinoma (HCC) who progressed on sorafenib treatment – Bruix J, et al

Key results

OS	Primary analysis		Updated analysis	
	Regorafenib (n=379)	Placebo (n=194)	Regorafenib (n=379)	Placebo (n=194)
Patients with event, n (%)	233 (61)	140 (72)	290 (77)	169 (87)
mOS, months (95%CI)	10.6 (9.1, 12.1)	7.8 (6.3, 8.8)	10.7 (9.1, 12.2)	7.9 (6.4, 9.0)
HR (95%CI); p-value	0.63 (0.50, 0.79); <0.0001		0.61 (0.50, 0.75); <0.0001	

Conclusion

- **The updated OS data confirm those of the primary OS data in the RESORCE trial and suggest that in patients with HCC regorafenib is an effective treatment option for those who have progressed on prior sorafenib**

Developed based on abstract only

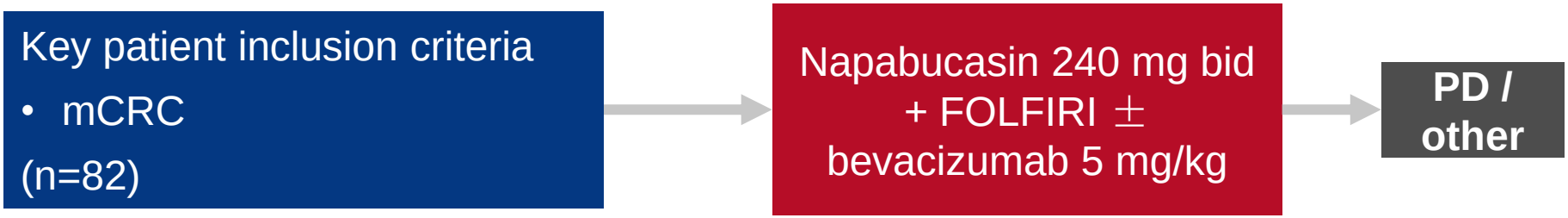
Bruix J, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-009

CANCERS OF THE COLON, RECTUM AND ANUS

LBA-003 Phase 1b/II study of cancer stemness inhibitor napabucasin in combination with FOLFIRI 1/2 bevacizumab (bev) in metastatic colorectal cancer (mCRC) patients (pts) – Bendell J*

Study objective

- To assess the efficacy and safety of napabucasin in combination with FOLFIRI ± bevacizumab in patients with mCRC



PRIMARY ENDPOINT

- Confirmation of RP2D

SECONDARY ENDPOINTS

- DCR, ORR, safety

*Presented by O'Neil BH; Developed based on abstract only

Bendell J, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-003

LBA-003 Phase 1b/II study of cancer stemness inhibitor napabucasin in combination with FOLFIRI 1/2 bevacizumab (bev) in metastatic colorectal cancer (mCRC) patients (pts) – Bendell J*

Key results

	DCR, n/N (%)		ORR, n/N (%)	
	Evaluable	ITT	Evaluable	ITT
All patients	55/66 (83)	55/82 (67)	14/66 (21)	14/82 (17)
≥2L FOLFIRI-naïve	33/39 (85)	33/50 (66)	8/39 (21)	8/50 (16)
≥2L FOLFIRI-exposed	22/27 (81)	22/32 (69)	6/27 (22)	6/32 (19)
2L FOLFIRI-naïve, GERCOR study†	24/59 (41)	24/69 (35)	3/59 (5)	3/69 (4)

- Grade 3 AEs: diarrhoea (n=15), fatigue (6), hypokalaemia (2), hyponatremia (1), hypophosphatemia (1), dehydration (1), abdominal pain (1), vomiting (1) and weight loss (1)
- Grade 4 AEs: diarrhoea (n=1)

Conclusion

- **Napabucasin + FOLFIRI ± bevacizumab demonstrated promising signs of efficacy and an acceptable safety profile in patients with pre-treated mCRC, including those who had previously received FOLFIRI ± bevacizumab**

*Presented by O'Neil BH; Developed based on abstract only

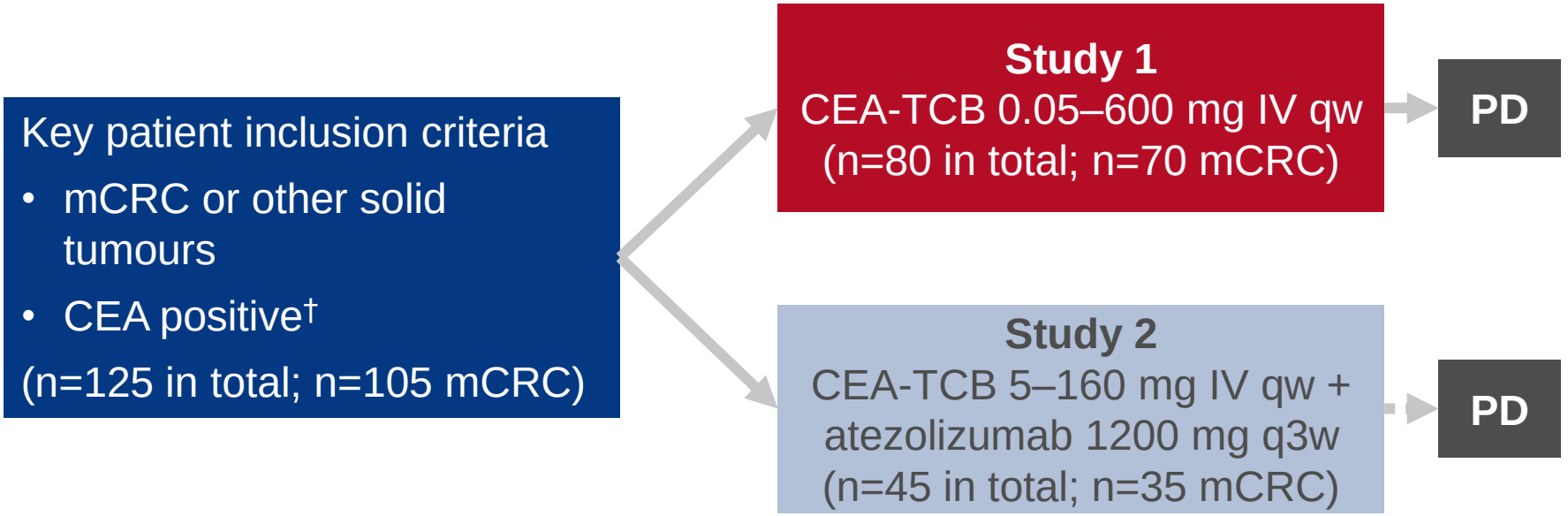
Bendell J, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-003

†Tournigand et al, 2004

LBA-004: Novel carcinoembryonic antigen T-cell bispecific (CEA-TCB) antibody: Preliminary clinical data as a single agent and in combination with atezolizumab in patients with metastatic colorectal cancer (mCRC) – Argilés G, et al

Study objective

- To assess the efficacy and safety of CEA-TCB* as monotherapy or in combination with atezolizumab in patients with mCRC in two phase 1 studies



*A novel T-cell bispecific antibody targeting CEA on tumour cells and CD3 on T cells; †≥20% of tumour cells with moderate or high CEA expression

Developed based on abstract only

Argilés G, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-004

LBA-004: Novel carcinoembryonic antigen T-cell bispecific (CEA-TCB) antibody: Preliminary clinical data as a single agent and in combination with atezolizumab in patients with metastatic colorectal cancer (mCRC) – Argilés G, et al

Key results

mCRC, n (%)	CEA-TCB (n=31)	CEA-TCB + atezolizumab (n=14)
Confirmed PR (RECIST v1.1)	2 (6)	3 (21.5)
SD* in MSS tumours	4 (13)	4 (29)
Metabolic PR at 4–6 weeks†	9 (29)	7 (50)

- The most common grade ≥3 TRAEs with CEA-TCB monotherapy were infusion-related reactions (24%) and diarrhoea (7%) with dose-limiting toxicities (DLT) observed in 5 patients
- There were no new toxicities with CEA-TCB + atezolizumab and 2 patients had DLTs
- For CEA-TCB monotherapy, biopsies demonstrated a 3.6-fold increase in Ki67 + CD3 T cells vs. baseline (p=0.035)

Conclusions

- **In patients with mCRC, CEA-TCB monotherapy demonstrated anti-tumour activity during dose escalation and CEA-TCB + atezolizumab showed enhanced activity and manageable safety**
- **The data for on-treatment increases of intratumoral CD3 T cells support the mechanism of action of CEA-TCB and suggest that it is the first tumour-targeted T cell bispecific agent with biological activity in a solid tumour indication**

Developed based on abstract only

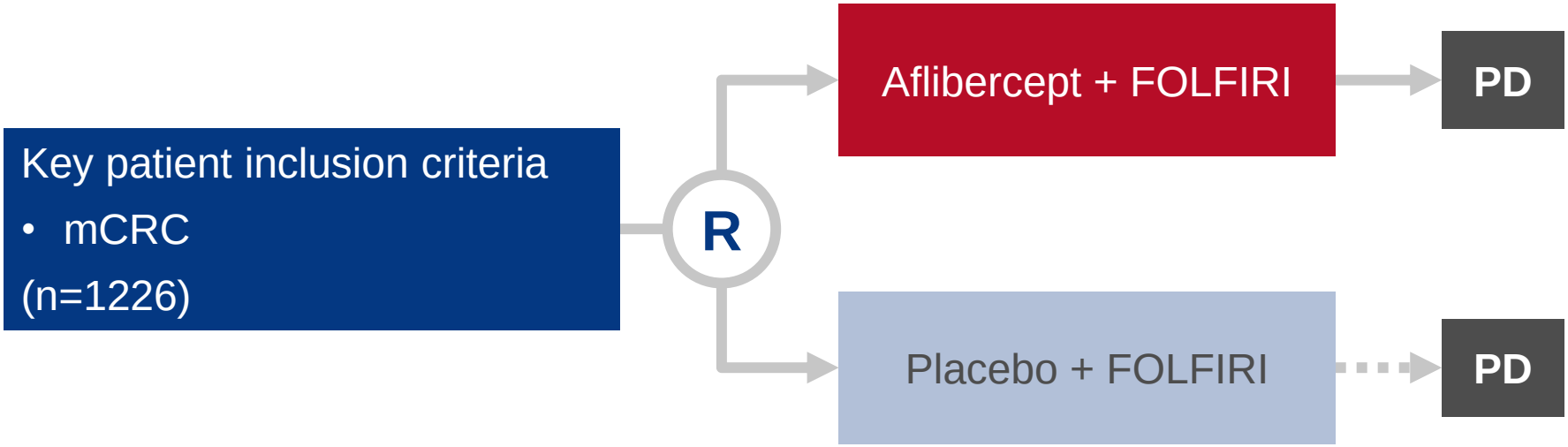
*Tumour reductions of 10–30%; †FDG PET, EORTC criteria

Argilés G, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-004

LBA-005: VELOUR trial biomarkers update: Impact of RAS, BRAF, and sidedness on aflibercept activity – Wirapati P*, et al

Study objective

- To evaluate the efficacy according to RAS/BRAF status and sidedness in patients with mCRC receiving FOLFIRI in combination with either aflibercept or placebo



- 666 patients had available tissue samples
- Suitable specimens were assessed for somatic mutation using NGS targeting extended RAS and BRAF genes (n=482 with non-missing values)
- Sidedness was extracted from available pathological reports

*Presented by Tejpar S; Developed based on abstract only

Wirapati P, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-005

LBA-005: VELOUR trial biomarkers update: Impact of RAS, BRAF, and sidedness on aflibercept activity – Wirapati P*, et al

Key results

- For the 482 patients with available data, OS was still significant with aflibercept vs. placebo: HR 0.80 (95%CI 0.65, 0.99)
  - Results were similar to the ITT population (n=1226): HR 0.82 (95%CI 0.71, 0.93)

Mutation	Status	n	mOS, months Aflibercept + FOLFIRI	mOS, months Placebo + FOLFIRI	HR (95%CI)	Interaction – ratio of HR (95%CI); p-value
KRASex2	WT	281	11.6	14.9	0.74 (0.56, 0.99)	1.21 (0.79, 1.86); 0.38
	MUT	201	10.6	12.6	0.90 (0.65, 1.24)	
ExtRAS	WT	218	11.7	16.0	0.70 (0.50, 0.97)	1.39 (0.90, 2.13); 0.13
	MUT	264	11.2	12.6	0.93 (0.70, 1.23)	
BRAF	WT	446	12.4	13.0	0.84 (0.67, 1.05)	0.49 (0.22, 1.09); 0.08
	MUT	36	5.5	10.3	0.42 (0.16, 1.09)	

Conclusions

- **There were no significant interactions observed in any of the mutation subgroups, although the ratios of treatment HR appear to favour RAS WT**
- **Similar findings have been observed in other trials of bevacizumab and ramucirumab**

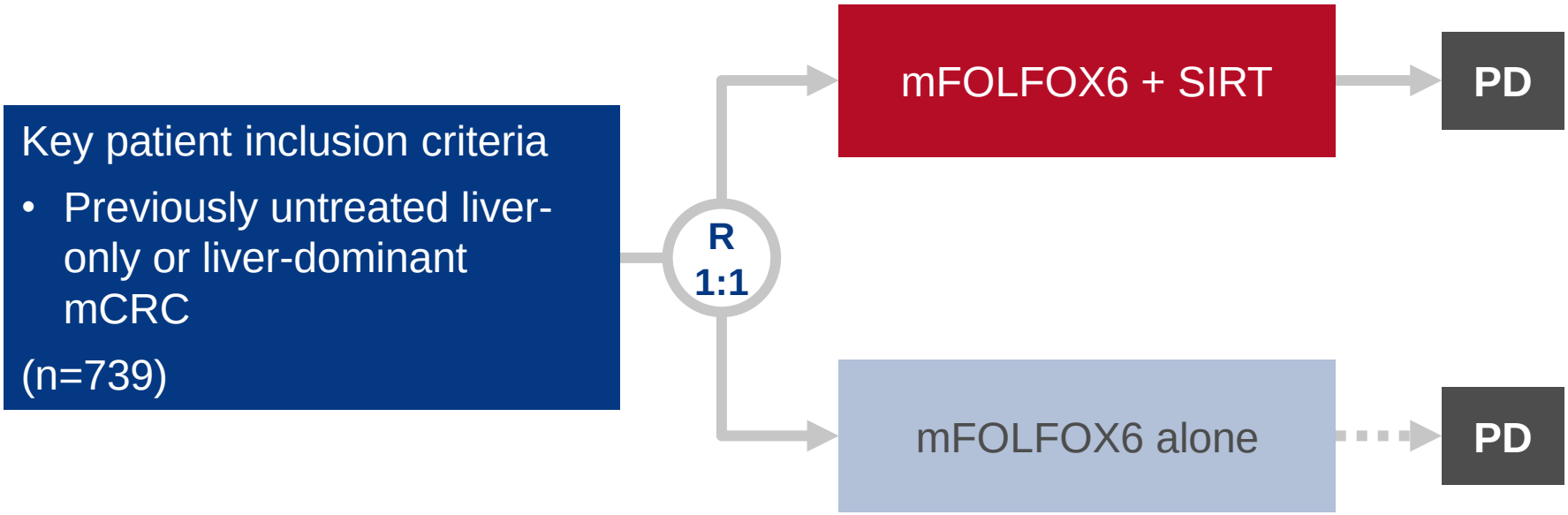
*Presented by Tejpar S; Developed based on abstract only

Wirapati P, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-005

LBA-006: Impact of primary tumour location on survival in patients with metastatic colorectal cancer receiving selective internal radiation therapy and chemotherapy as first-line therapy – van Hazel G, et al

Study objective

- To assess the efficacy and safety of 1L mFOLFOX6 ± SIRT according to primary tumour location in patients with mCRC, using data from two clinical trials*



PRIMARY ENDPOINTS

- PFS, OS

SECONDARY ENDPOINTS

- Safety

*SIRFLOX and FOXFIRE-Global

Developed based on abstract only

van Hazel G, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-006

LBA-006: Impact of primary tumour location on survival in patients with metastatic colorectal cancer receiving selective internal radiation therapy and chemotherapy as first-line therapy – van Hazel G, et al

Key results

	n	mFOLFOX6 + SIRT	mFOLFOX6 alone	HR (95%CI); p-value
mPFS, months				
Overall	739	11.1	10.6	NA (NA, NA); 0.22
Right-sided primary	179	10.8	8.7	0.73 (0.53, 1.01); 0.053
Left-sided primary	540	11.4	10.8	0.93 (0.78, 1.11); 0.426
mOS, months				
Overall	739	24.3	24.6	NA (NA, NA); 0.84
Right-sided primary	179	22.0	17.1	0.64 (0.46, 0.89); 0.007
Left-sided primary	540	24.6	25.6	1.12 (0.92, 1.36); 0.279

- The incidence of grade ≥3 AEs did not differ for right- vs. left-sided primary tumours (p>0.05)

Conclusions

- **In patients with mCRC, 1L mFOLFOX6 + SIRT was associated with significant improvements in OS for patients with right- but not left-sided primary tumours**
- **The FOXFIRE trial cohort will be used to validate these findings**

Developed based on abstract only

van Hazel G, et al. Ann Oncol 2017; 28 (suppl 3): abstr LBA-006

O-011: RET rearrangements define a new and rare molecular subtype of metastatic colorectal cancer (mCRC) – Pietrantonio F, et al

Study objective

- To identify and characterise RET fusions in mCRC and investigate their prognostic impact

Key inclusion criteria

- Metastatic disease
- *RET* fusion confirmed by RNA-sequencing/NGS (pre-screening with IHC/FISH not sufficient)

Sources of data	RET fusion partners
Ignyta's phase 1/1b study screening programme RXDX-105, NCT01877811)	*NCOA4-RET* (n=1)
	CCDC6-RET (n=1) Retrieval ongoing
Italian & Korean screening collaboration	*NCOA4-RET* (n=4)
	CCDC6-RET (n=1)
Foundation Medicine clinical database	*NCOA4-RET* (n=7)
	CCDC6-RET (n=6)
	TRIM24-RET (n=2)
	TNIP1-RET (n=1)

RET rearranged mCRC (n=22)

NCOA4-RET (n=12)
CCDC6-RET (n=7)
TRIM24-RET (n=2)
TNIP1-RET (n=1)

vs. non-rearranged cases screened at 3 referral centres in Milan, Pisa and Seoul

RET negative mCRC (n=236)

Pietrantonio F, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-011

O-011: RET rearrangements define a new and rare molecular subtype of metastatic colorectal cancer (mCRC) – Pietrantonio F, et al

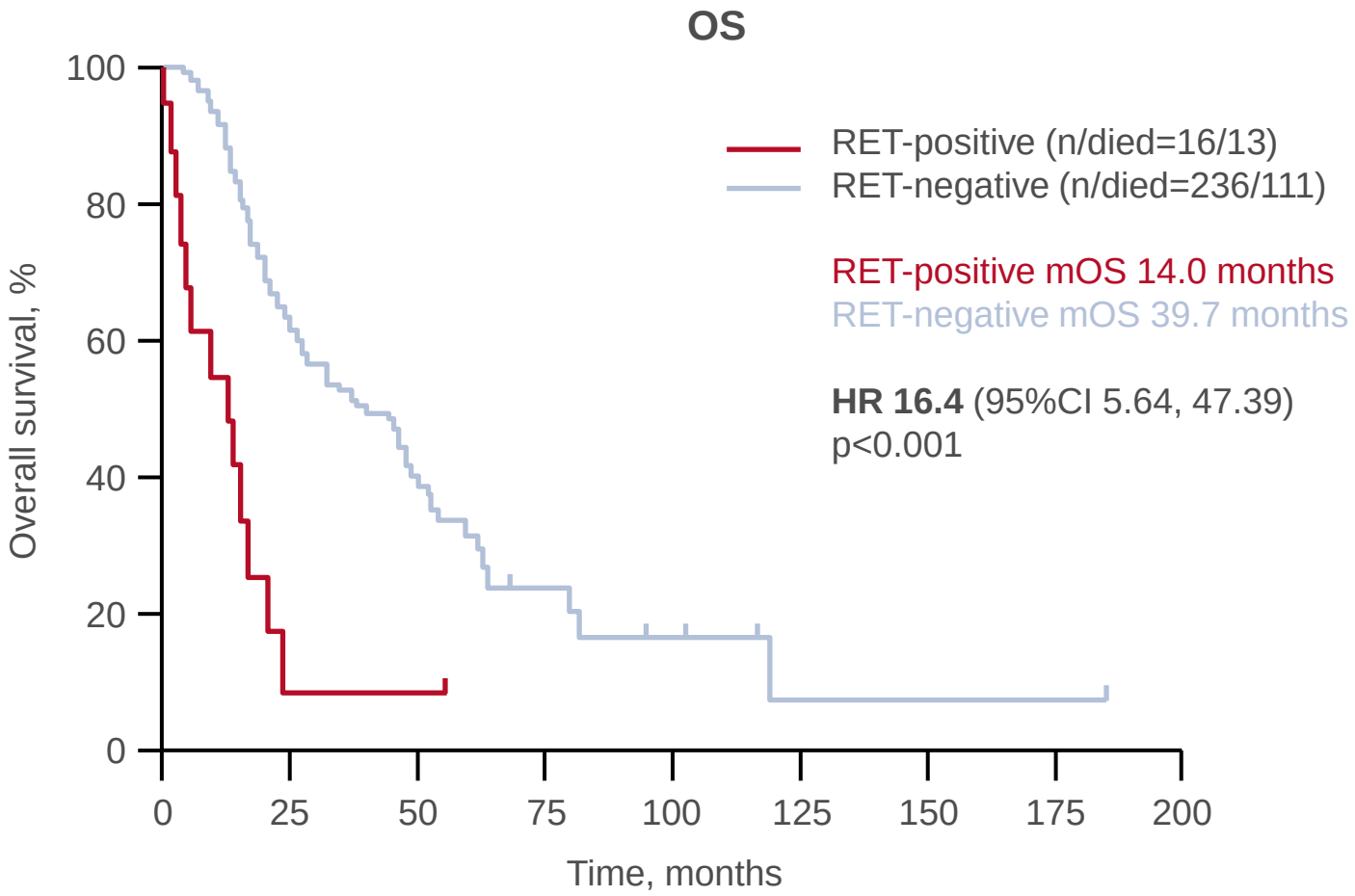
Key results

Characteristics		*RET* re-arranged (n=22), n (%)	*RET* negative (n=236), n (%)	p-value
Sex	Female Male	13 (59) 9 (41)	101 (43) 135 (57)	0.141
Age, years	Median (range)	66 (25–80)	60 (17–88)	**0.027**
Primary tumour location	**Right colon** Left colon Rectum NA	**10 (56)** 8 (44) 0 (0) 4	77 (33) 97 (41) 60 (26) -	**0.028**
Primary tumour resected	Yes No	8 (36) 14 (64)	181 (77) 55 (23)	**<0.001**
Time to metastases	Synchronous Metachronous	19 (86) 3 (14)	161 (68) 75 (32)	0.076
RAS and BRAF status	**All wild-type** *RAS* mutated *BRAF* mutated NA	**22 (100)** 0 (0) 0 (0) -	53 (26) 127 (62) 26 (13) 30	**<0.001**
MSI status	MSS **MSI-high** NA	12 (57) **9 (43)** 1	157 (92) 14 (8) 65	**<0.001**

Pietrantonio F, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-011

O-011: RET rearrangements define a new and rare molecular subtype of metastatic colorectal cancer (mCRC) – Pietrantonio F, et al

Key results (cont.)



Pietrantonio F, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-011

O-011: RET rearrangements define a new and rare molecular subtype of metastatic colorectal cancer (mCRC) – Pietrantonio F, et al

Key results (cont.)

Characteristics		Median, months	n	Univariate analysis			Multivariable model		
				HR	95%CI	p-value	HR	95%CI	p-value
RET status	Negative	39.7	236	1	–	**–**	1	–	**–**
	Rearranged	14.0	16	16.35	5.64, 47.39	**<0.001**	3.69	1.62, 8.44	**0.002**
Primary tumour site	Left colon / rectum	46.9	163	1	–	**–**	1	–	–
	Right colon	27.4	83	1.57	1.11, 2.48	**0.015**	1.54	0.96, 2.47	0.076
Age, years	<65	36.2	170	1	–	–	–	–	–
	>65	29.1	82	1.24	0.84, 1.89	0.269	–	–	–
Primary resection	Yes	45.7	186	1	–	**–**	1	–	**–**
	No	20.2	66	1.95	1.45, 3.68	**<0.001**	1.76	1.04, 2.96	**0.036**
Time to metastases	Metachronous	49.5	76	1	–	–	–	–	–
	Synchronous	27.4	176	1.39	0.93, 1.99	0.119	–	–	–
RAS and *BRAF* status	All wild-type	30.5	76	1	–	**–**	1	–	–
	RAS mutated	45.7	127	0.74	0.49, 1.09	**0.026**	0.77	0.48, 1.22	–
	BRAF mutated	18.0	26	1.45	0.83, 2.78		1.57	0.84, 2.90	0.447
MMR status	Proficient	45.7	165	1	–	**–**	1	–	–
	Deficient	20.0	21	1.73	0.97, 4.18	**0.061**	1.29	0.62, 2.66	0.498

Pietrantonio F, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-011

O-011: RET rearrangements define a new and rare molecular subtype of metastatic colorectal cancer (mCRC) – Pietrantonio F, et al

Conclusions

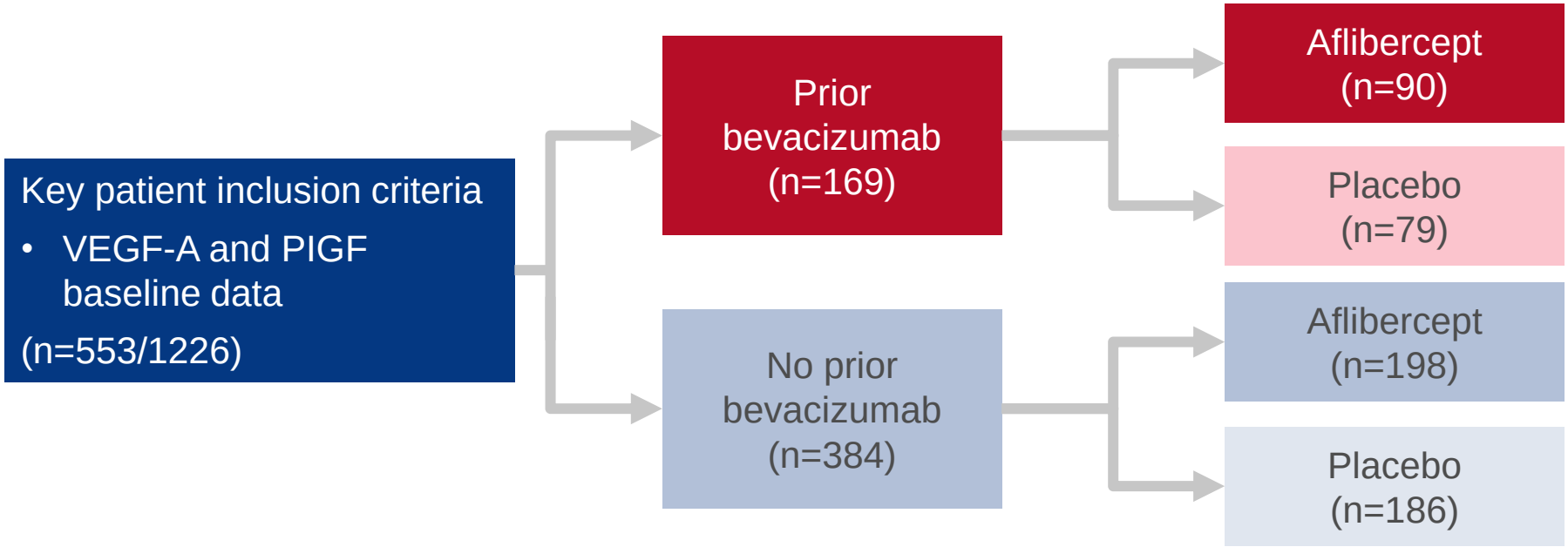
- ***RET*** **fusions occurred more often in older female patients with right-sided, *RAS* and *BRAF* wild-type mCRC**
- **MSI-high status was more frequent than expected in *RET* fusion-positive mCRC**
- ***RET*** **fusions have a negative impact on prognosis as they are independently associated with significantly shorter survival in both univariate and multivariate analysis**
- ***RET*** **fusions may offer a target for the development of personalised therapy**

Pietrantonio F, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-011

O-012: Impact of prior bevacizumab treatment of VEGFA and PIGF levels and patient outcomes: A retrospective analysis of baseline plasma samples from the VELOUR trial – Van Cutsem E, et al

Study objective

- To retrospectively evaluate growth factor levels and outcomes of aflibercept and prior bevacizumab in patients with mCRC from the VELOUR study



Van Cutsem E, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-012

O-012: Impact of prior bevacizumab treatment of VEGFA and PlGF levels and patient outcomes: A retrospective analysis of baseline plasma samples from the VELOUR trial – Van Cutsem E, et al

Key results

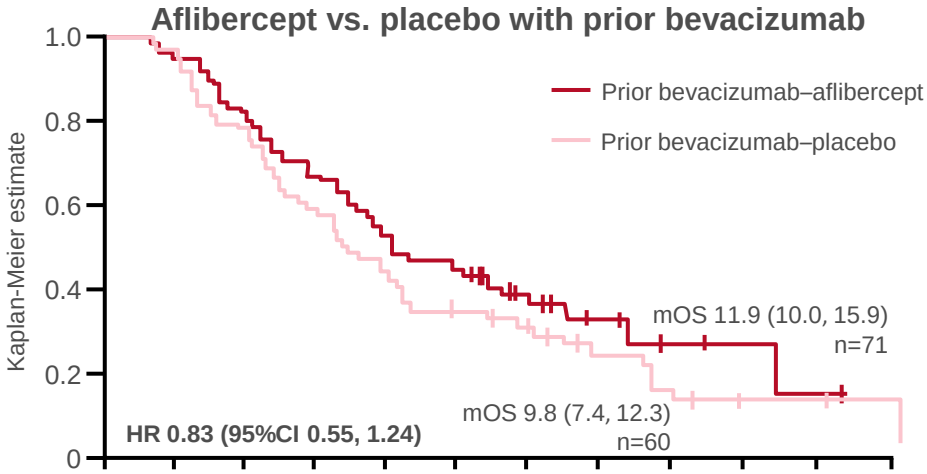
		Mean VEGF-A, pg/mL	Mean PlGF, pg/mL	mPFS, months (95%CI)	mOS, months (95%CI)	Aflibercept vs. placebo	
						Difference in OS, months	HR (95%CI)
Prior bevacizumab (n=169)	Aflibercept (n=90)	762.6	23.1	7.2 (5.7, 8.6)	12.1 (10.0, 16.4)	**1.5**	**0.84 (0.59, 1.19)**
	Placebo (n=79)	753.1	20.7	3.9 (3.0, 4.4)	10.6 (9.1, 12.5)		
No prior bevacizumab (n=384)	Aflibercept (n=198)	148.9	12.0	6.8 (6.0, 7.5)	12.9 (11.9, 15.7)	**1.5**	**0.80 (0.63, 1.01)**
	Placebo (n=186)	165.4	11.4	4.9 (4.2, 5.7)	11.4 (9.9, 12.7)		

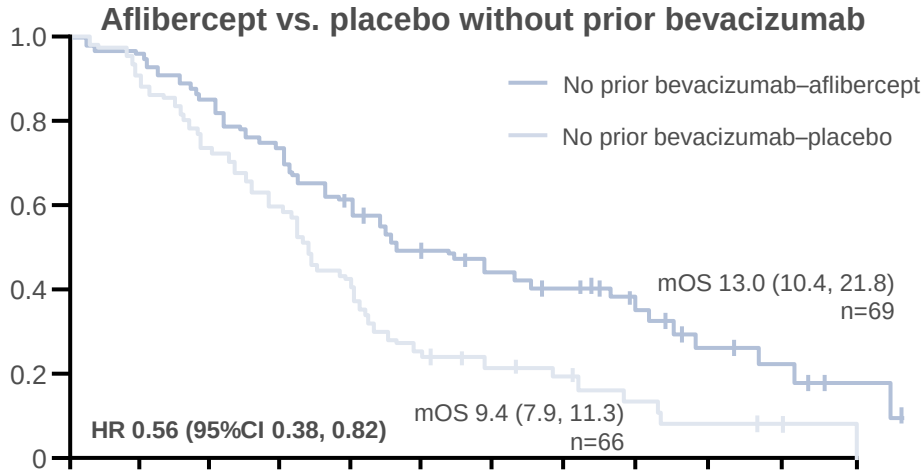
Van Cutsem E, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-012

O-012: Impact of prior bevacizumab treatment of VEGFA and PIGF levels and patient outcomes: A retrospective analysis of baseline plasma samples from the VELOUR trial – Van Cutsem E, et al

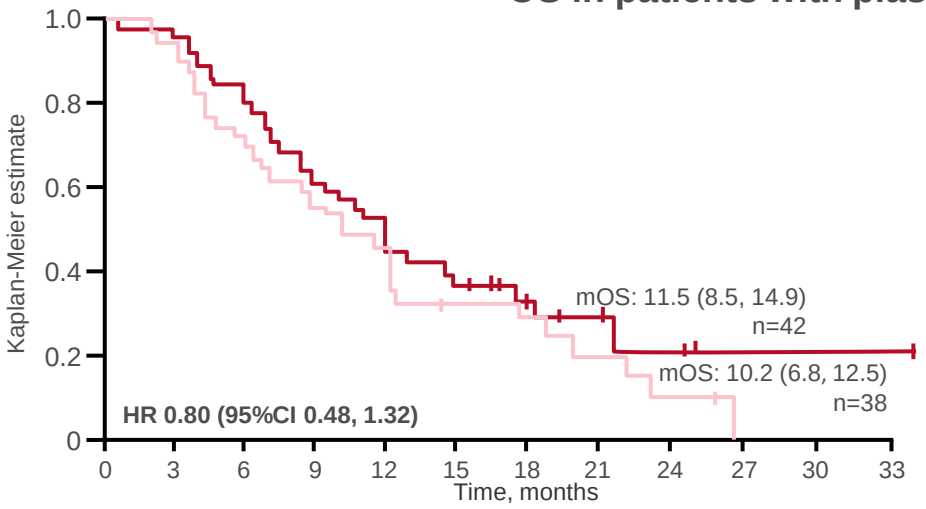
Key results (cont.)

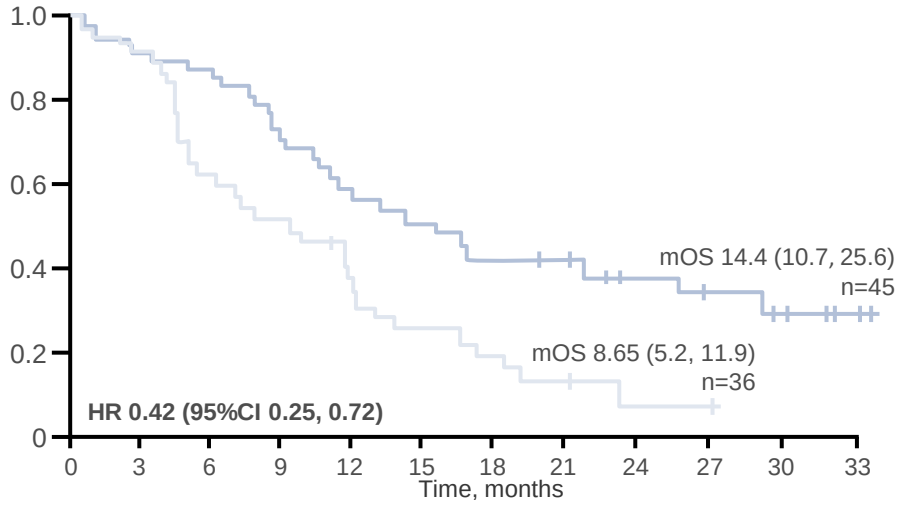
OS in patients with plasma VEGF-A above median





OS in patients with plasma PIGF above median





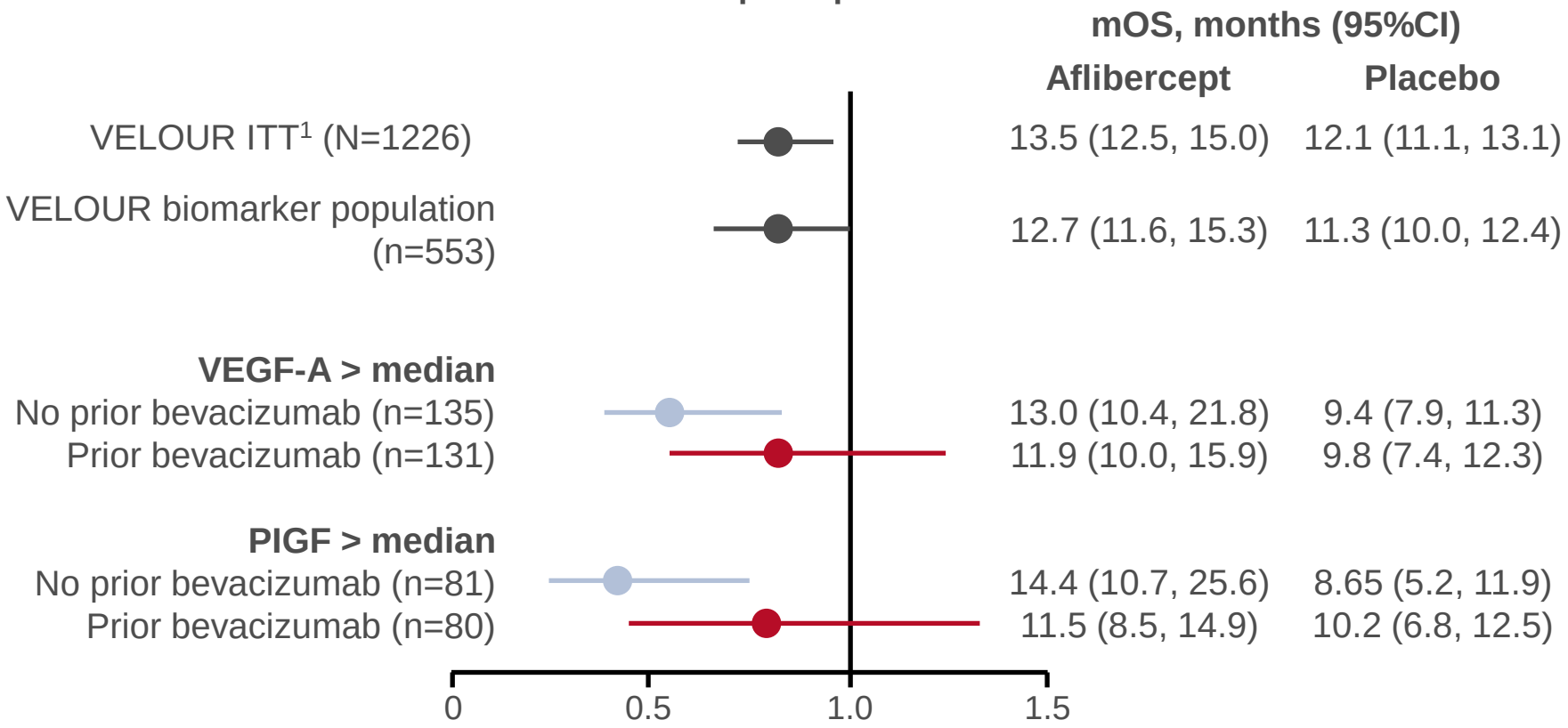
Van Cutsem E, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-012

O-012: Impact of prior bevacizumab treatment of VEGFA and PIGF levels and patient outcomes: A retrospective analysis of baseline plasma samples from the VELOUR trial – Van Cutsem E, et al

Key results (cont.)

OS in patients with VEGF-A or PIGF above median

Aflibercept vs. placebo



Retrospective evaluation of a limited dataset can only be hypothesis-generating

[1]Van Cutsem E, et al. *J Clin Oncol* 2012;30:3499–506.

Van Cutsem E, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-012

O-012: Impact of prior bevacizumab treatment of VEGFA and PlGF levels and patient outcomes: A retrospective analysis of baseline plasma samples from the VELOUR trial – Van Cutsem E, et al

Conclusions

- **Increased levels of cytokines, including VEGF-A and PlGF, occurred with prior treatment with 1L bevacizumab**
- **Aflibercept targets both VEGF-A and PlGF, and acts on both VEGFR1 and VEGFR2 with a higher affinity than bevacizumab so may help overcome bevacizumab-induced resistance**
- **Treatment with aflibercept + FOLFIRI was effective and was not affected by**
  - **Prior treatment with bevacizumab**
  - **VEGF-A or PlGF levels (high levels in bevacizumab naïve patients may suggest relatively higher activity)**
- **Further studies are required to investigate a potential role of aflibercept in patients with bevacizumab resistance**

Van Cutsem E, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-012

O-029: Central evaluation for surgical treatment options in FIRE-3 – updated results and impact on overall survival – Modest DP, et al

Study objective

- To determine the number of patients with mCRC who present with resectable disease during systemic 1L therapy and to correlate this with outcome

Methods

- FIRE-3 population
  - mCRC
  - Including KRAS/RAS wild type and mutations
  - Treated with FOLFIRI + cetuximab or FOLFIRI + bevacizumab
- Review population based on
  - Collected paired computed tomography scans (n=537)
  - Paired scans transformable into DICOM-format (n=488)
  - Scans allowed adequate assessment of lesions (n=448 included in project)
- Analysis
  - Baseline vs. best response images were evaluation in pairs by 8 surgeons and 3 medical oncologists
  - Definition of resectability: ≥50% votes for resectability

Modest DP, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-029

O-029: Central evaluation for surgical treatment options in FIRE-3 – updated results and impact on overall survival – Modest DP, et al

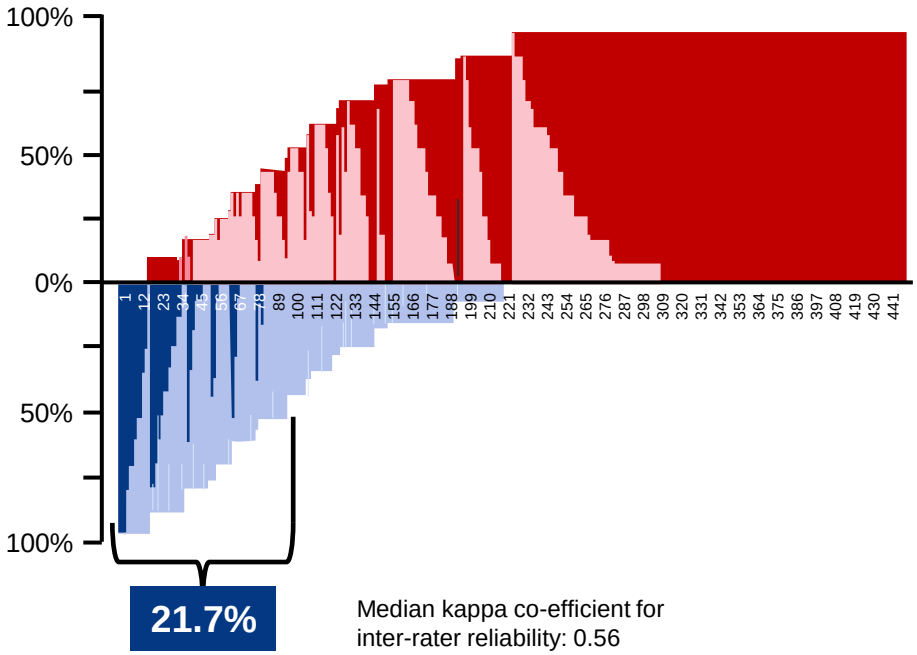
Key results

Votes for resectability at baseline

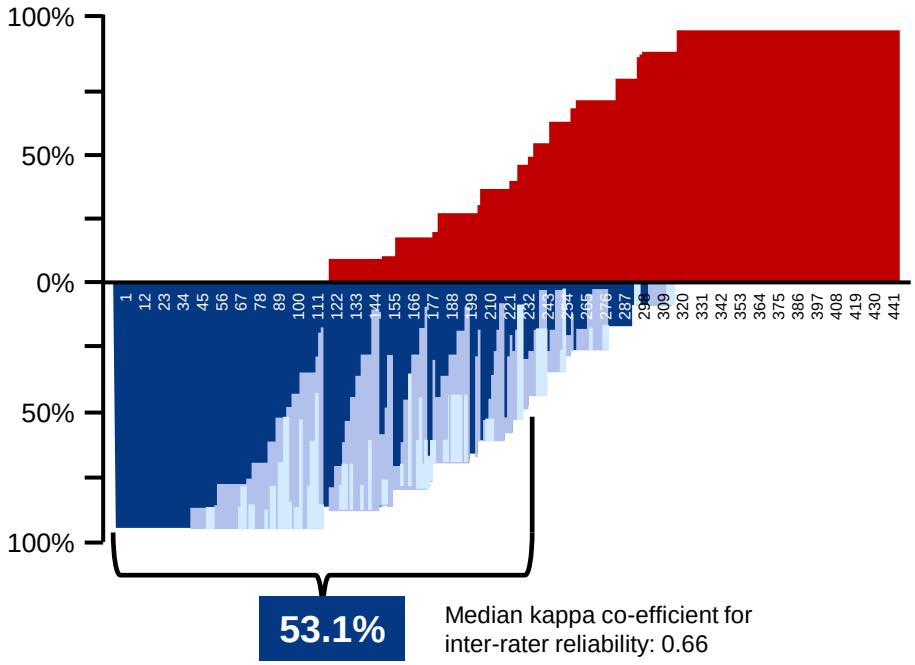
Votes for resectability at best response

Intention

- Not resectable
- Conversion possible[1]
- Abdominal lesions resectable[2]
- R0-resection[3]
- R0-resection all lesions



Median kappa co-efficient for inter-rater reliability: 0.56



Median kappa co-efficient for inter-rater reliability: 0.66

1. May be only abdominal lesions; 2. +/- perioperative chemotherapy at baseline and +/- locoregional therapy at best response; 3. with perioperative chemotherapy at baseline and including locoregional therapy all lesions

Modest DP, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-029

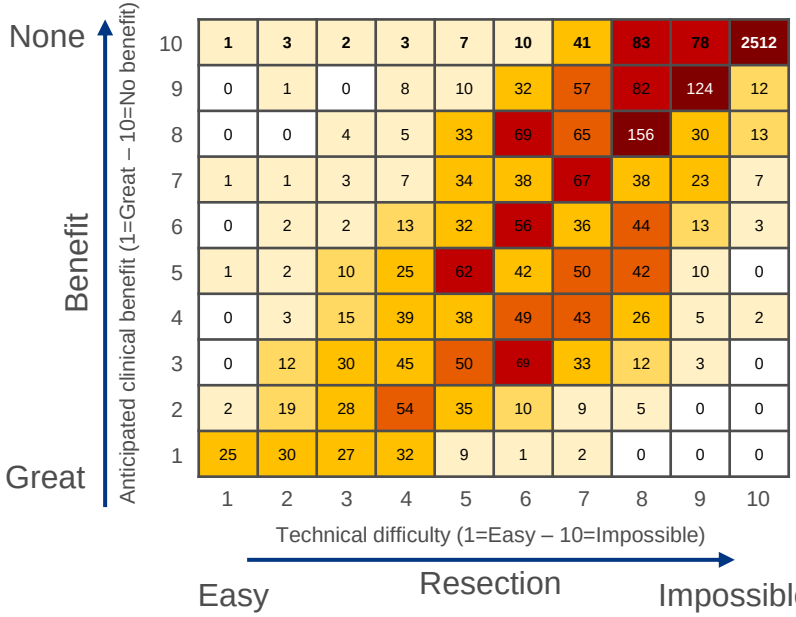
O-029: Central evaluation for surgical treatment options in FIRE-3 – updated results and impact on overall survival – Modest DP, et al

Key results (cont.)

Each number represents the number of distinct voting-combination of 1 reviewer concerning 1 patient

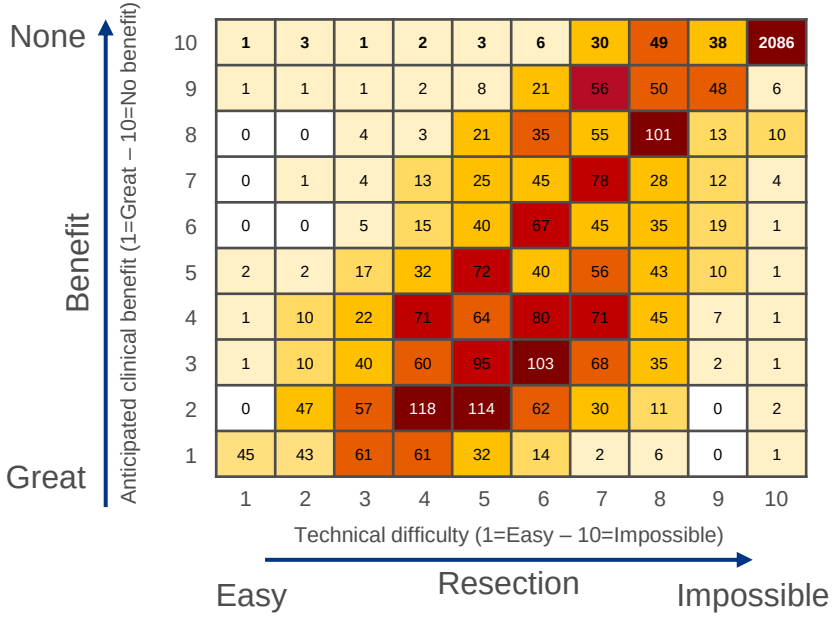
Evaluation at "baseline"

Evaluations of surgical interventions at best response.
4867 votes on 448 patients (10.86 votes/patient)



Evaluation at "best response"

Evaluations of surgical interventions at best response.
4860 votes on 448 patients (10.85 votes/patient)



The location within the heat map was derived from two scores:

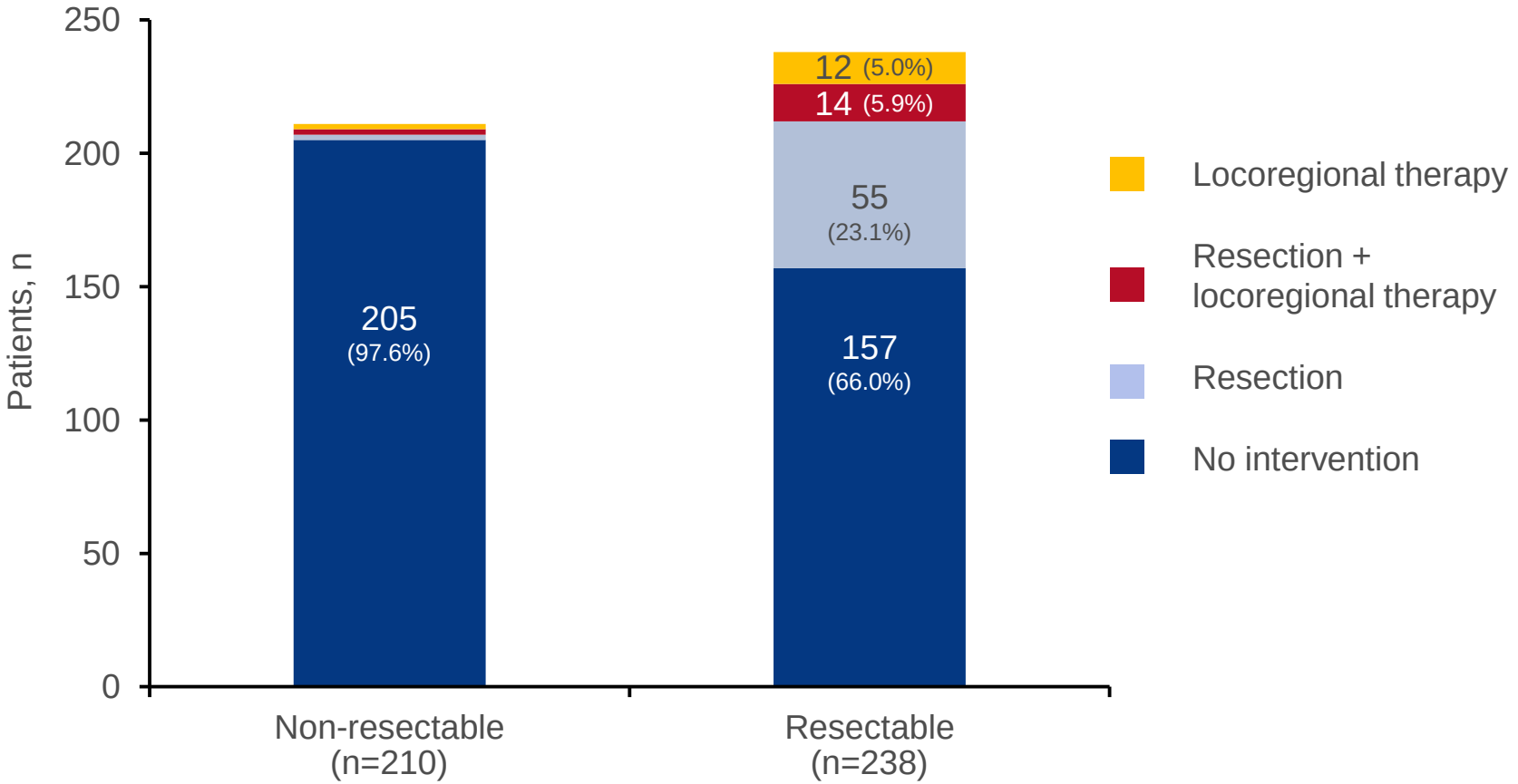
1. How difficult would a potential resection be? 1=easy, 10=impossible
2. Do you anticipate clinical benefit from resection? 1=great, 10=no benefit

Modest DP, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-029

O-029: Central evaluation for surgical treatment options in FIRE-3 – updated results and impact on overall survival – Modest DP, et al

Key results (cont.)

Intervention rates among non-resectable and resectable patients (review vs. study reports)



Modest DP, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-029

O-029: Central evaluation for surgical treatment options in FIRE-3 – updated results and impact on overall survival – Modest DP, et al

Conclusions

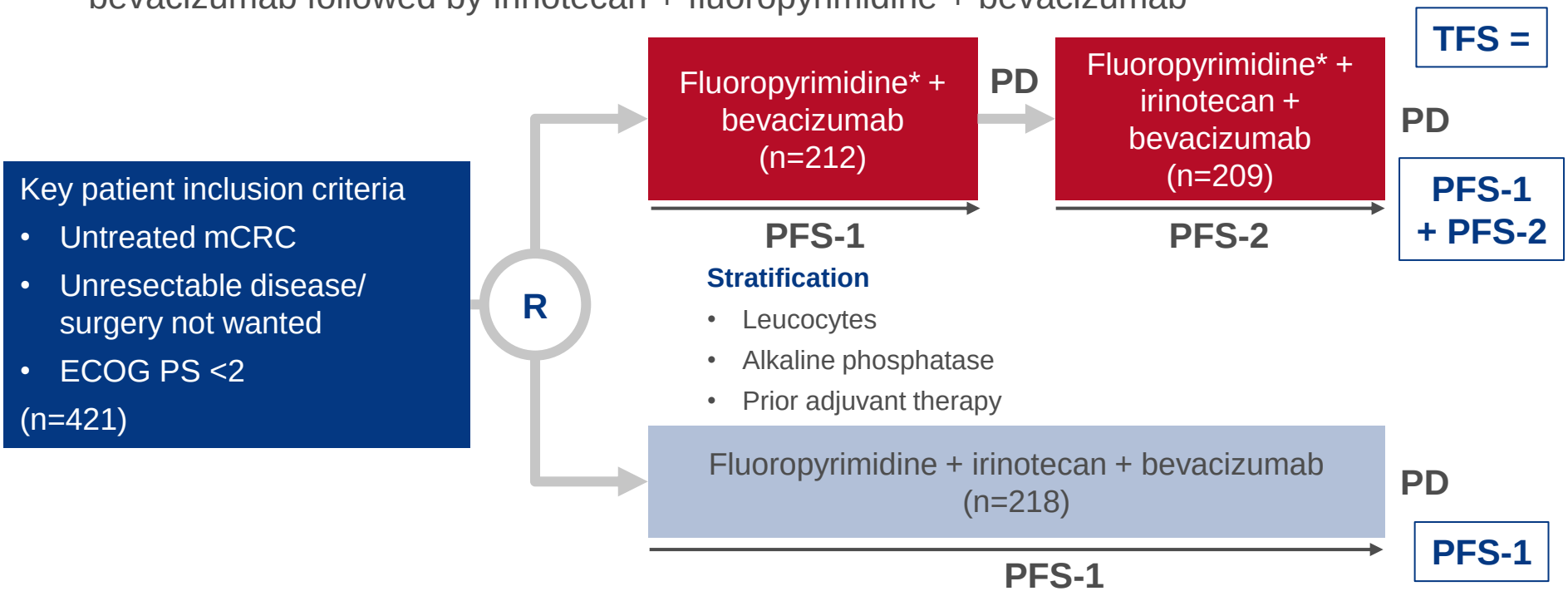
- **Resectability increased from 22% at baseline to 53% at best response**
- **Potential resections were voted as “easier” with a “greater” potential benefit at best response compared with baseline evaluations**
- **Only approximately a third of the patients who were identified as resectable at best response actually underwent any intervention**
- **These data suggest that approximately every second patient should have been considered for resection of metastases following treatment resectable disease**
- **It suggests that there may be a critical shortage concerning access to surgery and underlines the need for careful evaluation of patients**

Modest DP, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-029

O-026: Randomized phase III study of fluoropyrimidine (FP) plus bevacizumab (BEV) vs. FP plus irinotecan (IRI) and BEV as first-line therapy for metastatic colorectal cancer (mCRC): German AIO KRK0110 (ML22011)-study – Modest D, et al

Study objective

- Non-inferiority study to investigate the sequential application of fluoropyrimidine + bevacizumab followed by irinotecan + fluoropyrimidine + bevacizumab



PRIMARY ENDPOINT

- TFS

SECONDARY ENDPOINTS

- ORR, PFS-1, OS, QoL, safety

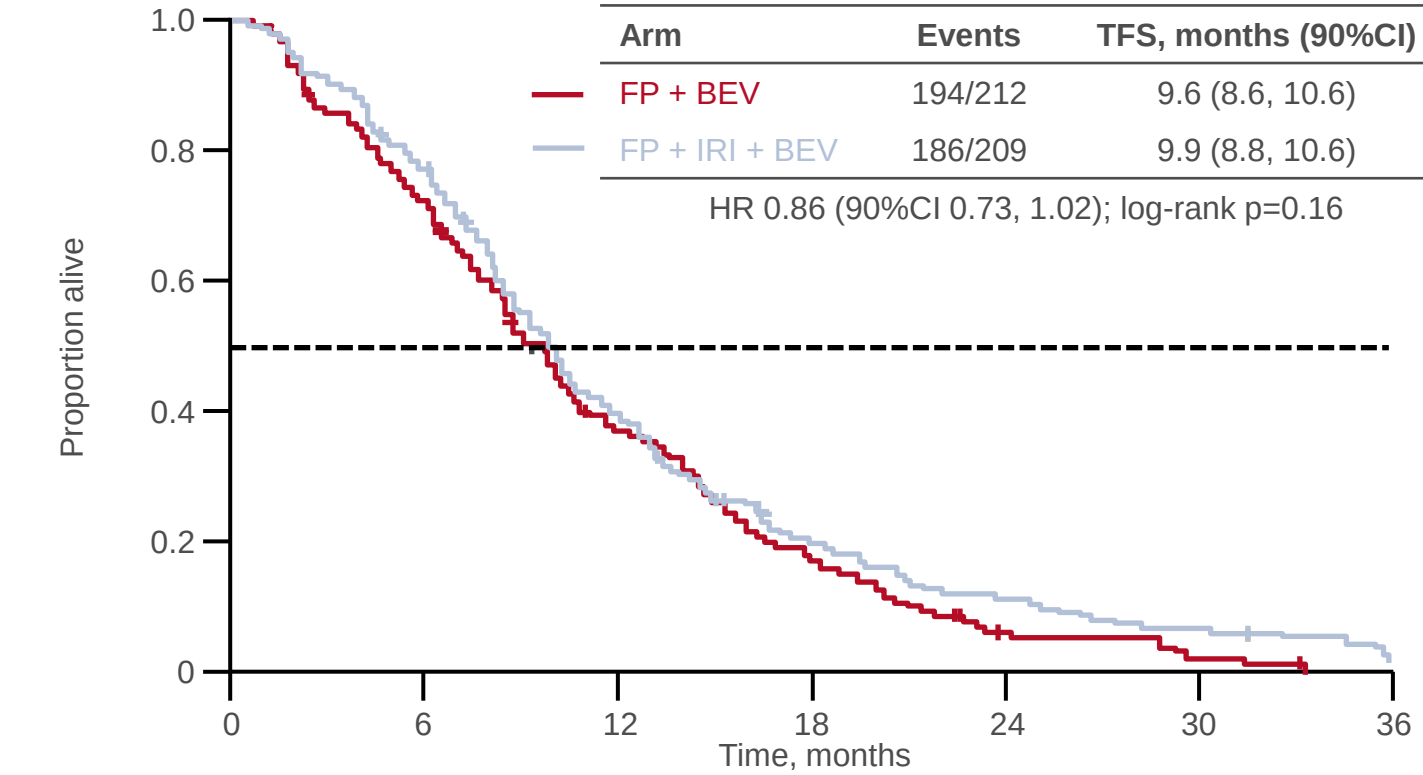
*Restricted to capecitabine from 2010 to 2013; investigator's choice 2013 to 2016

Modest D, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-026

O-026: Randomized phase III study of fluoropyrimidine (FP) plus bevacizumab (BEV) vs. FP plus irinotecan (IRI) and BEV as first-line therapy for metastatic colorectal cancer (mCRC): German AIO KRK0110 (ML22011)-study – Modest D, et al

Key results

Time to failure of strategy



Arm	Events	TFS, months (90%CI)
FP + BEV	194/212	9.6 (8.6, 10.6)
FP + IRI + BEV	186/209	9.9 (8.8, 10.6)

HR 0.86 (90%CI 0.73, 1.02); log-rank p=0.16

No. at risk						
FP + BEV	212	147	72	34	9	3
FP + IRI + BEV	209	153	78	35	19	10

Modest D, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-026

O-026: Randomized phase III study of fluoropyrimidine (FP) plus bevacizumab (BEV) vs. FP plus irinotecan (IRI) and BEV as first-line therapy for metastatic colorectal cancer (mCRC): German AIO KRK0110 (ML22011)-study – Modest D, et al

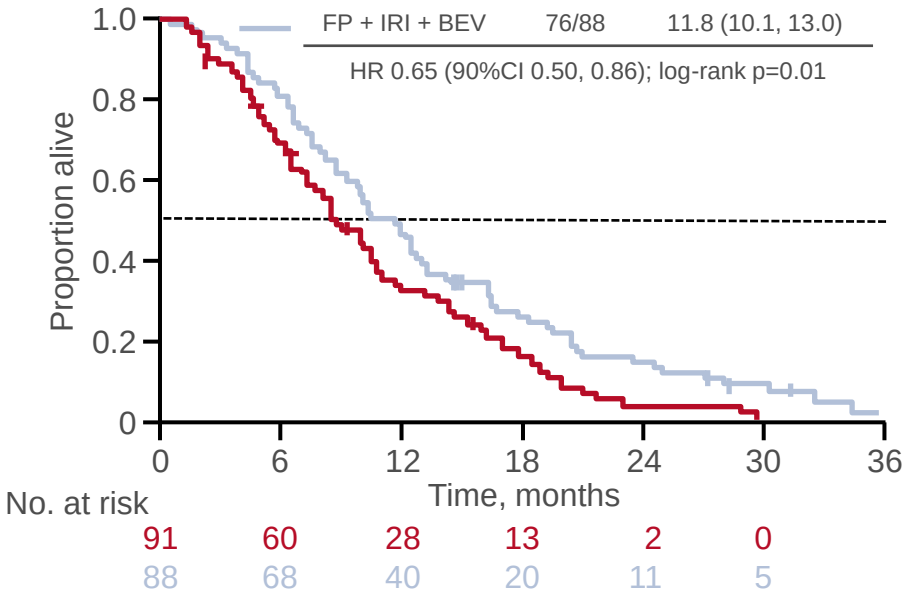
Key results (cont.)

Time to failure of strategy (subgroups)

RAS wild-type tumours

Arm	Events	TFS, months (90%CI)
FP + BEV	83/91	8.6 (7.6, 10.6)
FP + IRI + BEV	76/88	11.8 (10.1, 13.0)

HR 0.65 (90%CI 0.50, 86); log-rank p=0.01



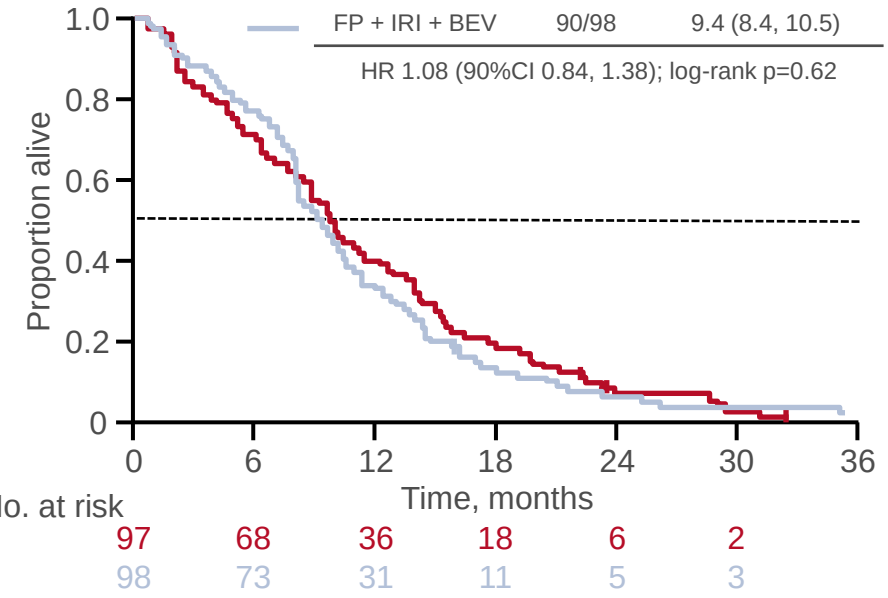
No. at risk

FP + BEV	91	60	28	13	2	0
FP + IRI + BEV	88	68	40	20	11	5

RAS mutant tumours

Arm	Events	TFS, months (90%CI)
FP + BEV	90/97	10.0 (8.8, 11.7)
FP + IRI + BEV	90/98	9.4 (8.4, 10.5)

HR 1.08 (90%CI 0.84, 1.38); log-rank p=0.62



No. at risk

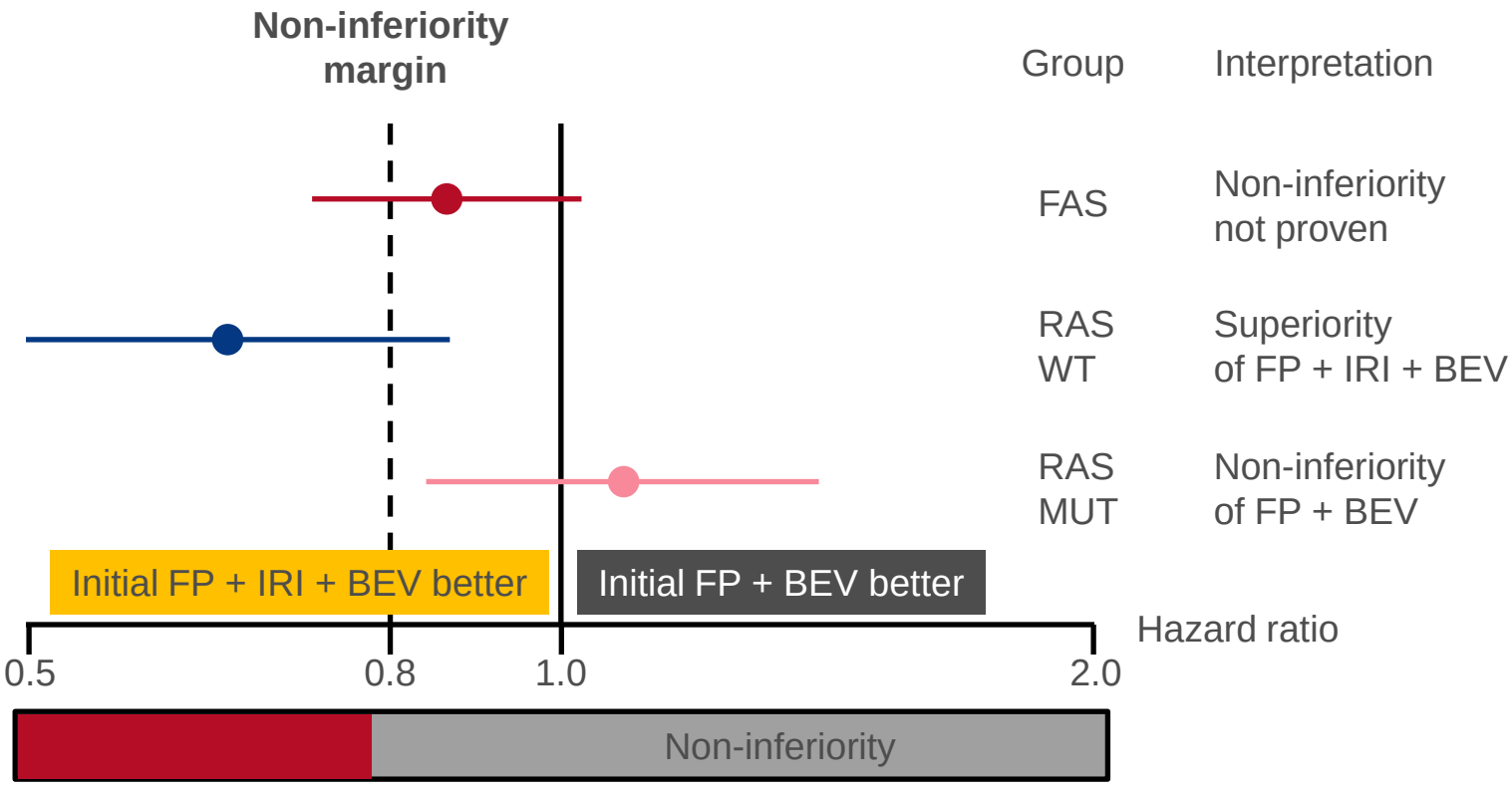
FP + BEV	97	68	36	18	6	2
FP + IRI + BEV	98	73	31	11	5	3

Modest D, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-026

O-026: Randomized phase III study of fluoropyrimidine (FP) plus bevacizumab (BEV) vs. FP plus irinotecan (IRI) and BEV as first-line therapy for metastatic colorectal cancer (mCRC): German AIO KRK0110 (ML22011)-study – Modest D, et al

Key results (cont.)

Time to failure of strategy – overview



Cox model interaction-test for study arm *RAS status: p=0.03

Modest D, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-026

O-026: Randomized phase III study of fluoropyrimidine (FP) plus bevacizumab (BEV) vs. FP plus irinotecan (IRI) and BEV as first-line therapy for metastatic colorectal cancer (mCRC): German AIO KRK0110 (ML22011)-study – Modest D, et al

Conclusions

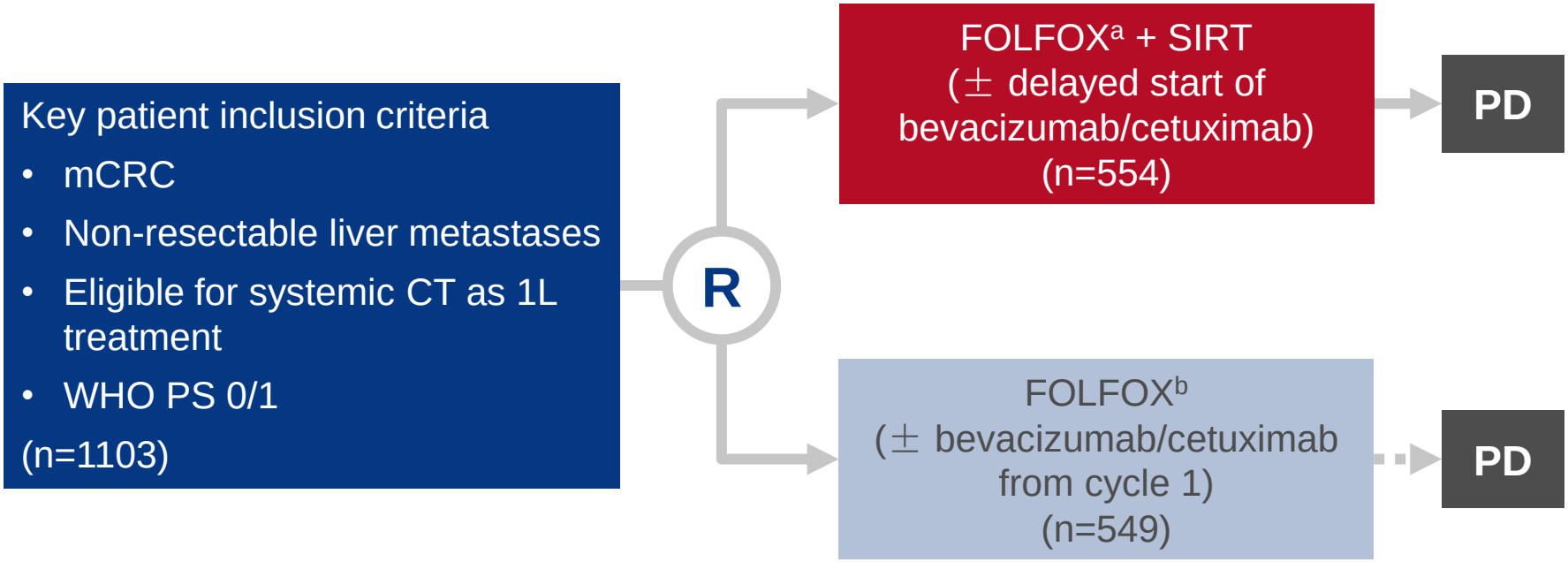
- The primary endpoint (TFS) was not met so non-inferiority of initial fluoropyrimidine + bevacizumab as compared with fluoropyrimidine + irinotecan + bevacizumab was not demonstrated
- Patients with RAS wild type mCRC did show benefit from upfront therapy with the intensive regimen (fluoropyrimidine + irinotecan + bevacizumab)
- The more intensive 1L regimen was not associated with a substantial improvement in outcome in patients with RAS mutant mCRC; these patients might be better treated with sequential therapy starting with fluoropyrimidine + bevacizumab

Modest D, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-026

O-027: Overall survival analysis of the FOXFIRE-SIRFLOX-FOXFIRE global prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer – Wasan H, et al

Study objective

- To evaluate the efficacy and safety of SIRT using yttrium-90 resin microspheres plus 1L CT in patients with unresectable mCRC



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- PFS at any site, liver-specific PFS, objective tumour response rate, safety

[a]Oxaliplatin 85 mg/m^2; [b]oxaliplatin 60 mg/m^2 to cycle 3 then oxaliplatin 85 mg/m^2

Wasan H, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-027

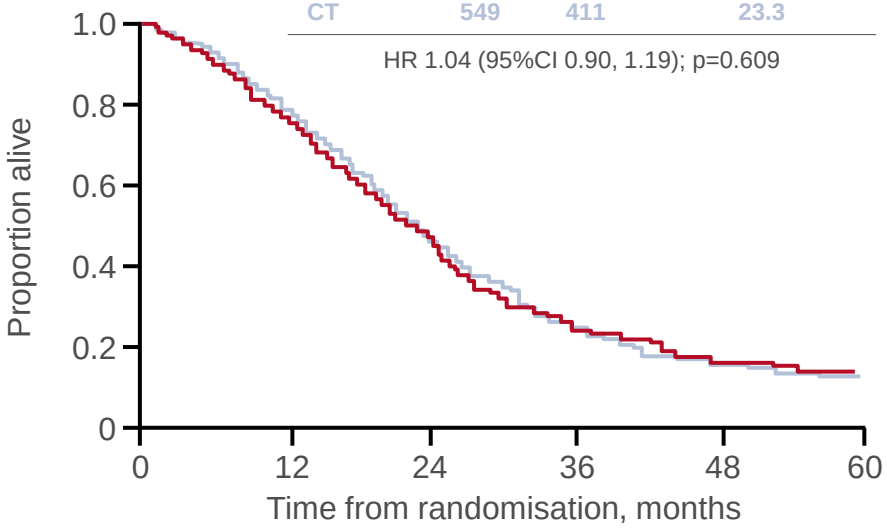
O-027: Overall survival analysis of the FOXFIRE-SIRFLOX-FOXFIRE global prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer – Wasan H, et al

Key results

OS (n=1103)

Arm	n	Events	Median, months
CT + SIRT	554	433	22.6
CT	549	411	23.3

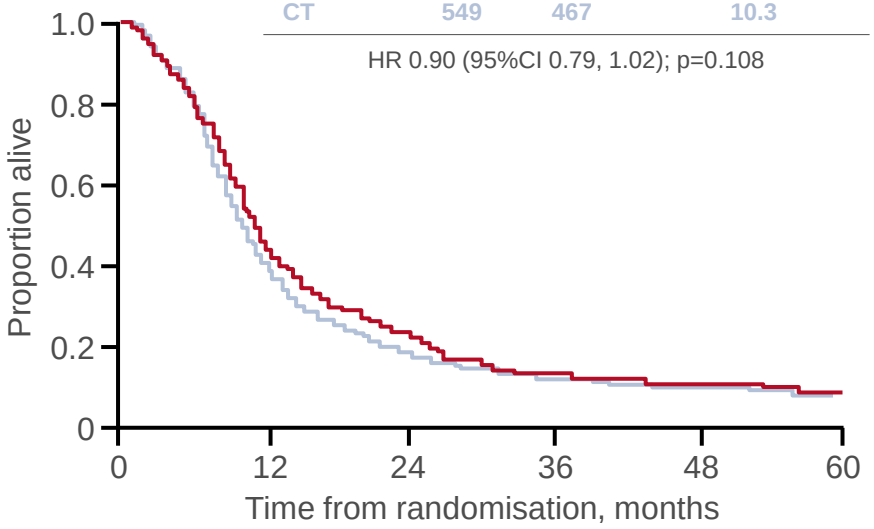
HR 1.04 (95%CI 0.90, 1.19); p=0.609



PFS

Arm	n	Events	Median, months
CT + SIRT	554	474	11.0
CT	549	467	10.3

HR 0.90 (95%CI 0.79, 1.02); p=0.108



No. at risk

CT + SIRT	554	417	247	91	35	17	554	229	104	37	15	7
CT	549	419	242	88	33	12	549	209	78	37	14	6

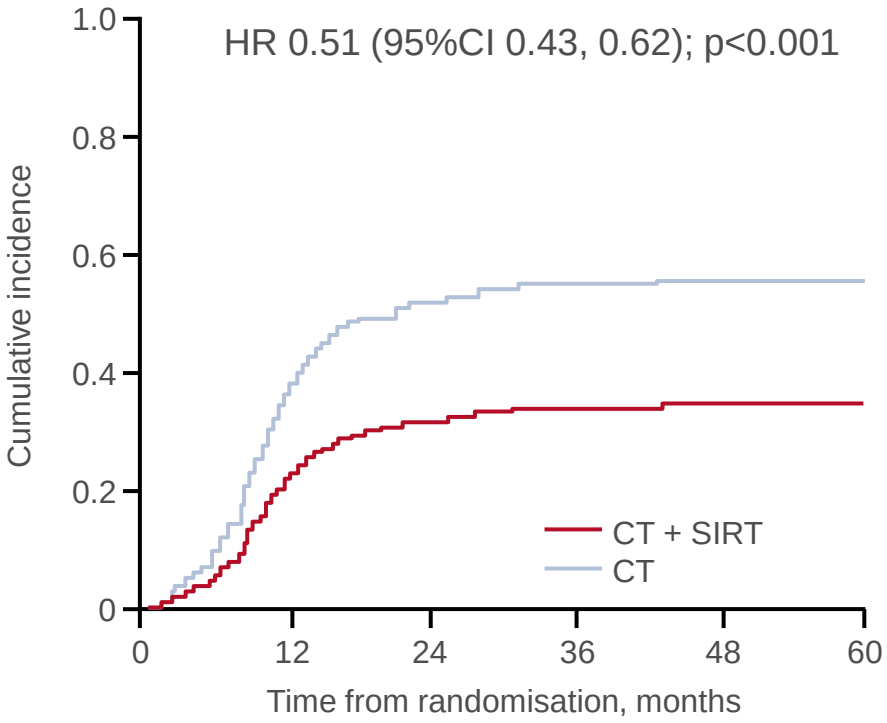
Wasan H, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-027

O-027: Overall survival analysis of the FOXFIRE-SIRFLOX-FOXFIRE global prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer – Wasan H, et al

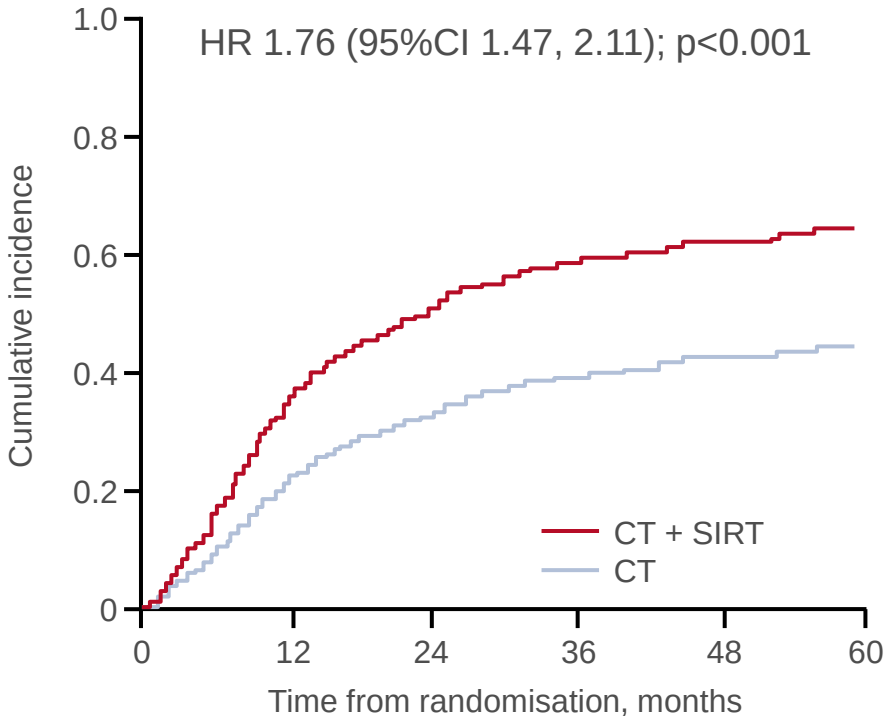
Key results (cont.)

Liver-specific PFS

First radiological progression within the liver



First progression extrahepatic or death without radiological progression having been documented



Wasan H, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-027

O-027: Overall survival analysis of the FOXFIRE-SIRFLOX-FOXFIRE global prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer – Wasan H, et al

Key results (cont.)

Selected all-cause AEs (safety population)

Adverse events. %	CT + SIRT (n=507)	CT (n=571)
All patients any grade	99.8	99.6
All patients grade ≥3	**74.0**	**66.5**
All patients grade 5	2.0	1.9
Haematological (grade ≥3)		
Neutropenia	**36.7**	**24.2**
Febrile neutropenia	**6.5**	**2.8**
Thrombocytopenia	**7.7**	**1.2**
Leukopenia	**5.9**	**2.3**
Non-haematological (grade ≥3)		
Fatigue	**8.5**	**4.9**
Abdominal pain	**6.1**	**2.3**
Diarrhoea	6.7	6.5
Peripheral neuropathy	**3.6**	**5.8**
SIRT associated events (grade ≥3)		
Radiation hepatitis	0.8	–
Gastric ulcer	0.8	–
Duodenal ulcer	0.6	–

Wasan H, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-027

O-027: Overall survival analysis of the FOXFIRE-SIRFLOX-FOXFIRE global prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer – Wasan H, et al

Conclusions

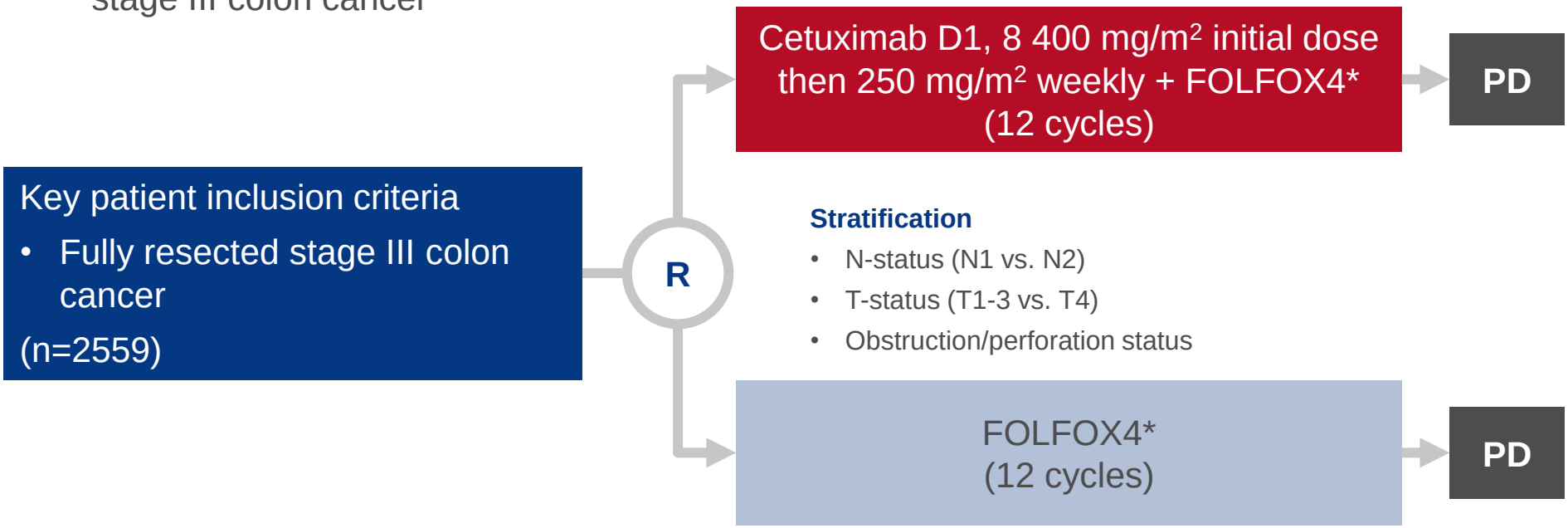
- **Addition of SIRT to 1L FOLFOX CT did not lead to any improvement in PFS (primary endpoint) or OS**
- **Significant benefit of adding SIRT was observed in PFS specific to the liver**
- **Toxicity, particularly for haematological AEs, was higher in the FOLFOX + SIRT group**

Wasan H, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-027

O-015: Prognostic value of primary tumor location in stage III colon cancer is associated with RAS and BRAF mutational status – Taieb J, et al

Study objective

- To investigate the impact of primary location on prognosis in patients with fully resected stage III colon cancer



- Primary tumour site was characterised as proximal (right; n=755) or distal (left; n=1114) to the splenic flexure

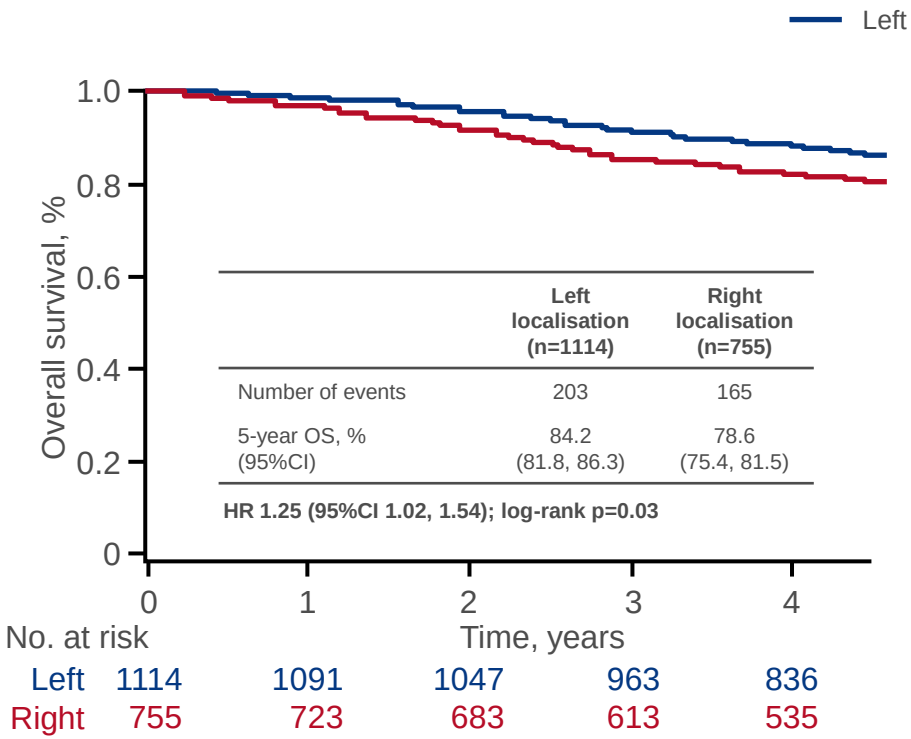
*Oxaliplatin 85 mg/m^2 D1, leucovorin 200 mg/m^2, 5FU bolus 400 mg/m^2 followed by 600 mg/m^2 22-hour IV D1, 2 q2w

Taieb J, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-015

O-015: Prognostic value of primary tumor location in stage III colon cancer is associated with RAS and BRAF mutational status – Taieb J, et al

Key results

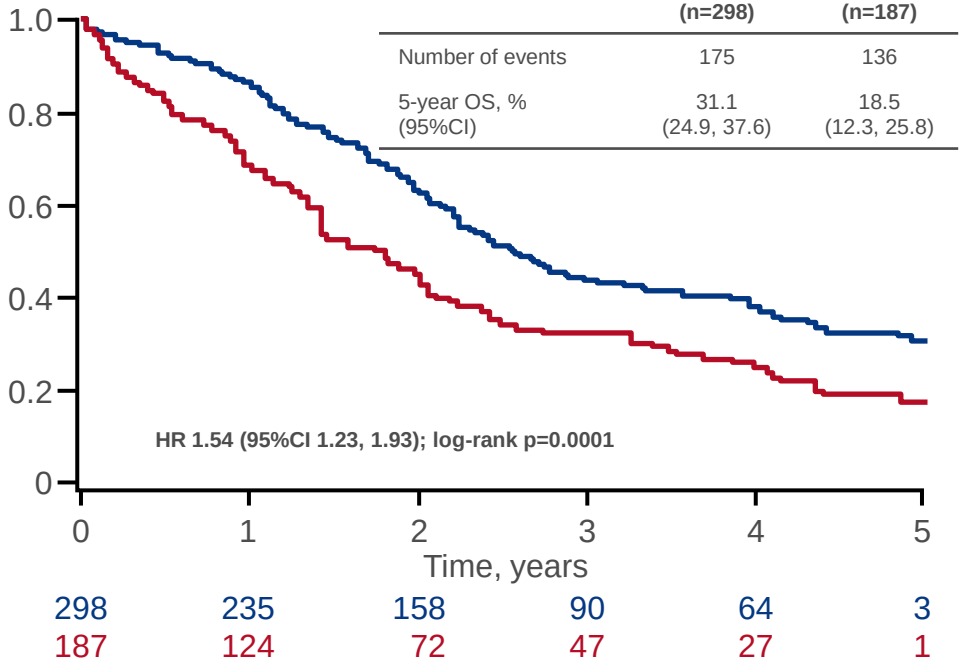
OS in right- and left-sided CRC



	Left localisation (n=1114)	Right localisation (n=755)
Number of events	203	165
5-year OS, % (95%CI)	84.2 (81.8, 86.3)	78.6 (75.4, 81.5)

No. at risk					
Left	1114	1091	1047	963	836
Right	755	723	683	613	535

SAR in right- and left-sided CRC



	Left localisation (n=298)	Right localisation (n=187)
Number of events	175	136
5-year OS, % (95%CI)	31.1 (24.9, 37.6)	18.5 (12.3, 25.8)

Left	298	235	158	90	64	3
Right	187	124	72	47	27	1

Taieb J, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-015

O-015: Prognostic value of primary tumor location in stage III colon cancer is associated with RAS and BRAF mutational status – Taieb J, et al

Key results (cont.)

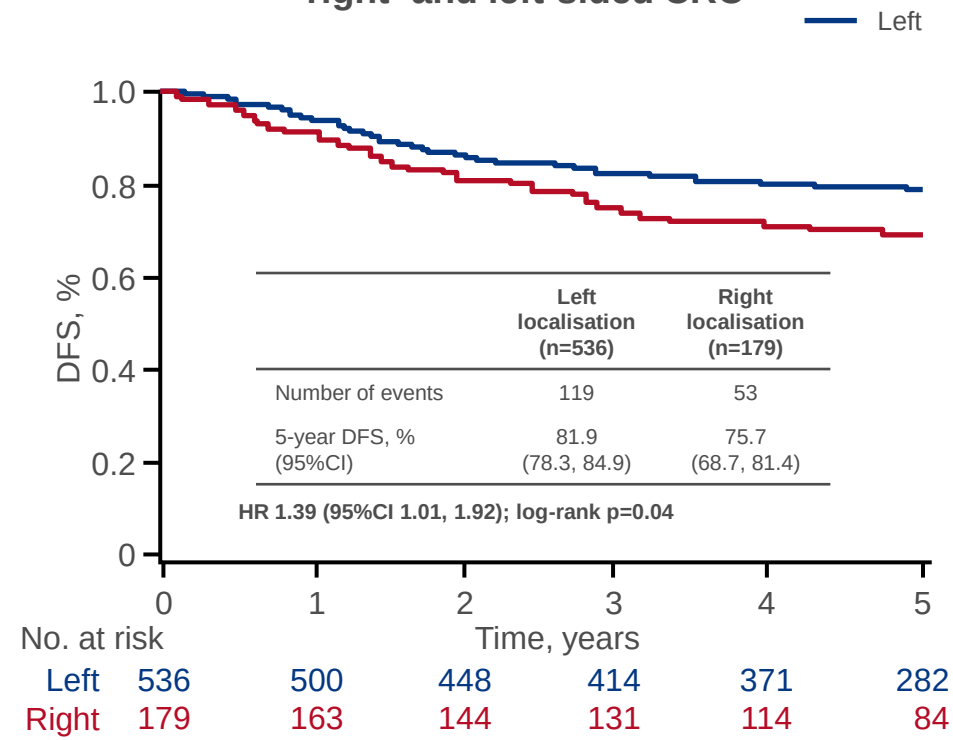
Prognostic factors by multivariate analysis	DFS, HR (95%CI); p-value	OS, HR (95%CI); p-value	SAR, HR (95%CI); p-value
Primary tumour location	0.91 (0.747, 1.11);	1.22 (0.96, 1.55);	1.48 (1.13, 1.92);
Right vs. left	0.33	0.11	0.005
Histopathology grade	1.36 (1.08, 1.71);	1.45 (1.10, 1.90);	1.49 (1.12, 1.98);
3–4 vs. 1–2	0.009	0.008	0.006
ECOG PS	1.33 (1.07, 1.65);	1.45 (1.12, 1.87);	1.15 (0.86, 1.54);
1–2 vs. 0	0.009	0.0047	0.33
pT	2.28 (1.41, 3.66);	2.59 (1.37, 4.89);	1.61 (0.71, 3.65);
pT 3–4 vs. pT 1–2	0.0007	0.003	0.26
pN	2.0 (1.66, 2.40);	2.12 (1.69, 2.66);	1.38 (1.07, 1.80);
pN2 vs. pN1	<0.0001	<0.0001	0.015
Bowel obstruction and perforation	1.31 (1.05, 1.62);	1.30 (1.00, 1.69);	1.08 (0.80, 1.45);
Bowel obstruction and/or perforation vs. no bowel and no perforation	0.015	0.05	0.61
MMR status	1.41 (0.97, 2.05);	1.62 (1.03, 2.56);	1.21 (0.72, 2.04);
MMR proficient vs. MMR deficient	0.076	0.037	0.47
***RAS/BRAF* status**			
RAS mutated vs. double WT	1.56 (1.27, 1.92); <0.0001	1.54 (1.19, 1.98); 0.0009	1.31 (0.98, 1.76); 0.07
BRAF mutated vs. double WT	1.28 (0.91, 1.79); 0.16	1.39 (0.93, 2.07) 0.10	1.81 (1.20, 2.75); 0.005

Taieb J, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-015

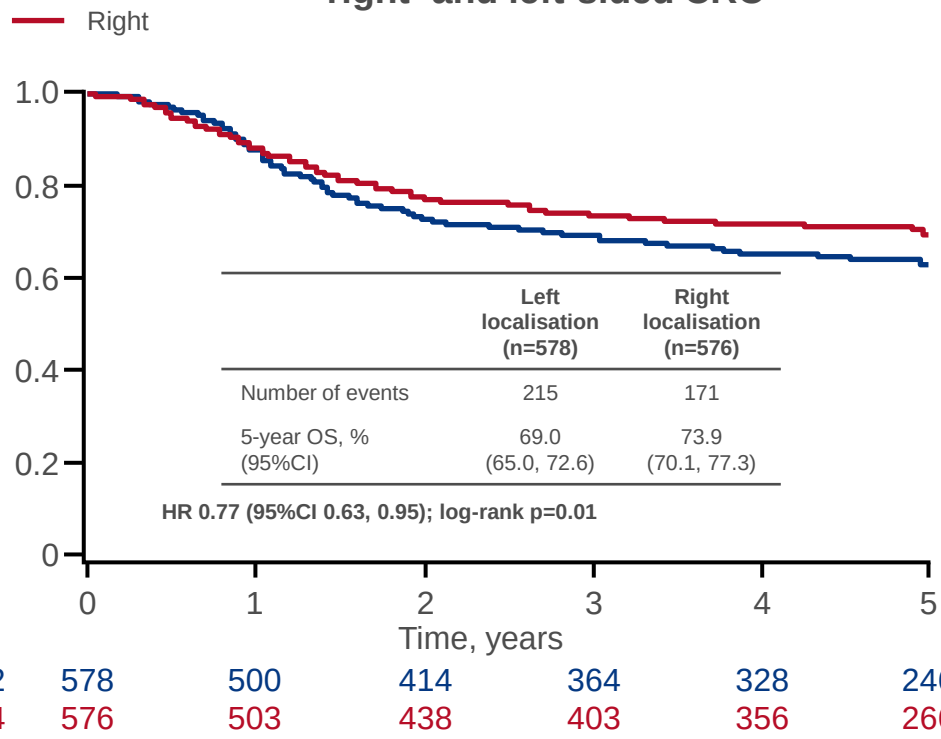
O-015: Prognostic value of primary tumor location in stage III colon cancer is associated with RAS and BRAF mutational status – Taieb J, et al

Key results (cont.)

DFS in double wild-type right- and left-sided CRC



DFS in *RAS* or *BRAF*-mutated right- and left-sided CRC



No. at risk												
Left	536	500	448	414	371	282	578	500	414	364	328	246
Right	179	163	144	131	114	84	576	503	438	403	356	266

Taieb J, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-015

O-015: Prognostic value of primary tumor location in stage III colon cancer is associated with RAS and BRAF mutational status – Taieb J, et al

Conclusions

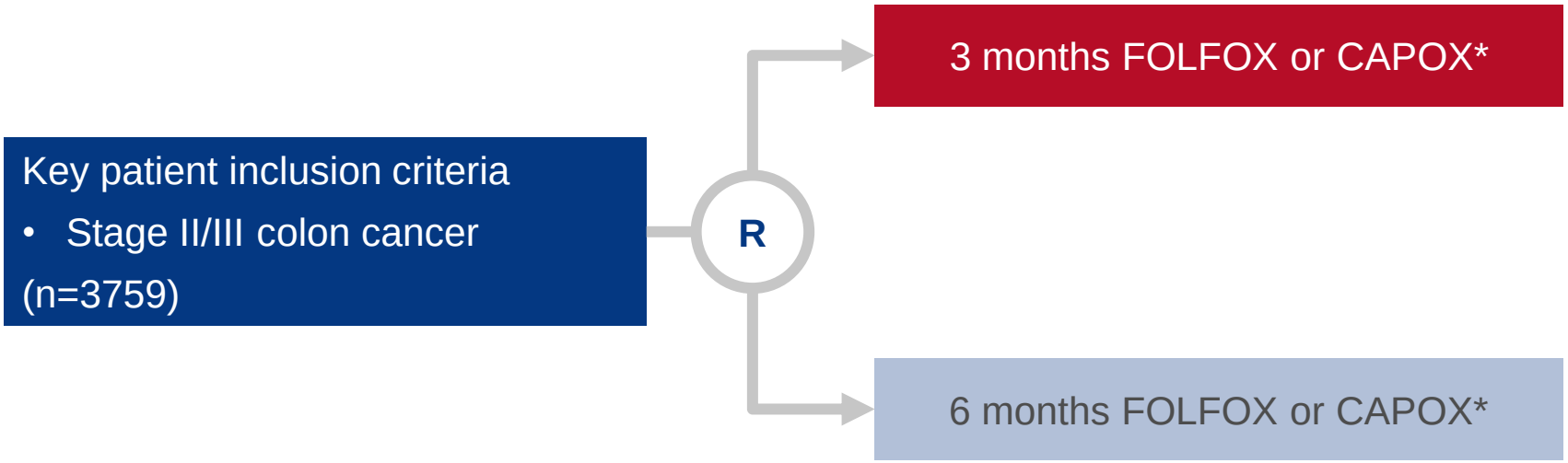
- **Patients with right-sided tumours showed worse survival with shorter OS and survival after relapse than those with left-sided tumours**
- **DFS is not affected by sidedness across the overall population**
- **However, analysis by *RAS* and *BRAF* mutation revealed**
  - **Shorter DFS in double wild-type patients**
  - **Longer DFS in patients harbouring *RAS*/*BRAF* mutations**

Taieb J, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-015

O-025: FOLFOX4/XELOX in stage II–III colon cancer: Early survival data of the Italian Three Or Six Colon Adjuvant (TOSCA) trial – Labianca R, et al

Study objective

- To test for non-inferiority of a shorter than standard adjuvant oxaliplatin-treatment (3 vs. 6 months) in patients with colon cancer



PRIMARY ENDPOINT

- Relapse-free survival

*Physician's choice

Labianca R, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-025

O-025: FOLFOX4/XELOX in stage II–III colon cancer: Early survival data of the Italian Three Or Six Colon Adjuvant (TOSCA) trial – Labianca R, et al

Key results

	Grade 1–2, %		Grade 3–4, %		
Adverse events	3 months	6 months	3 months	6 months	p-value[1]
Neurological	37.0	41.0	9.0*	31.0*	<0.0001
Febrile neutropenia	1.7	3.5	1.4	2.7	<0.0001
Thrombocytopenia	33.0	47.0	1.6	2.1	<0.0001
Diarrhoea	29.0	35.0	5.1	6.4	<0.0001
Allergic reactions	3.4	6.4	0.5	2.0	<0.0001

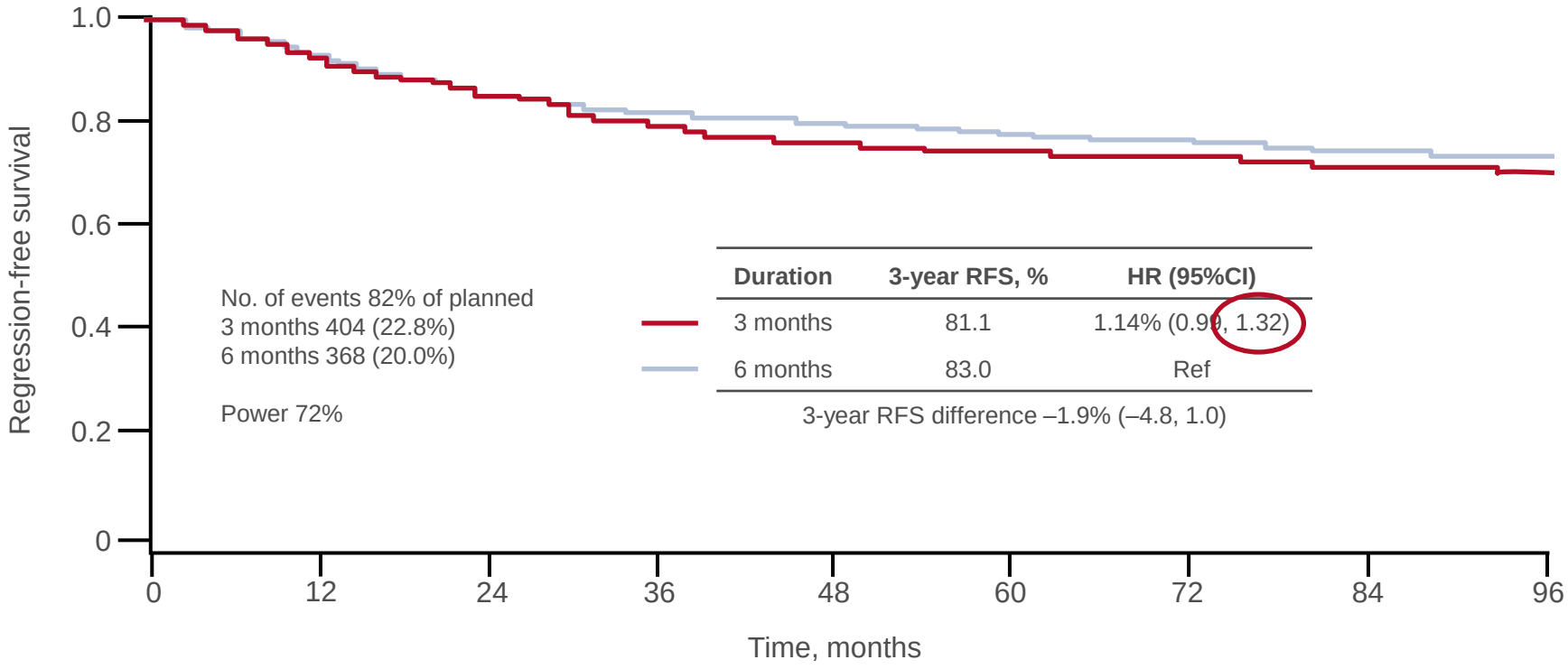
[1]Chi-squared test for trend; Total number of grade 5 events: 2 (possible)
*Clinically relevant neurological toxicity (grade 2, 3 and 4)

Labianca R, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-025

O-025: FOLFOX4/XELOX in stage II–III colon cancer: Early survival data of the Italian Three Or Six Colon Adjuvant (TOSCA) trial – Labianca R, et al

Key results (cont.)

RFS by arm (overall population)



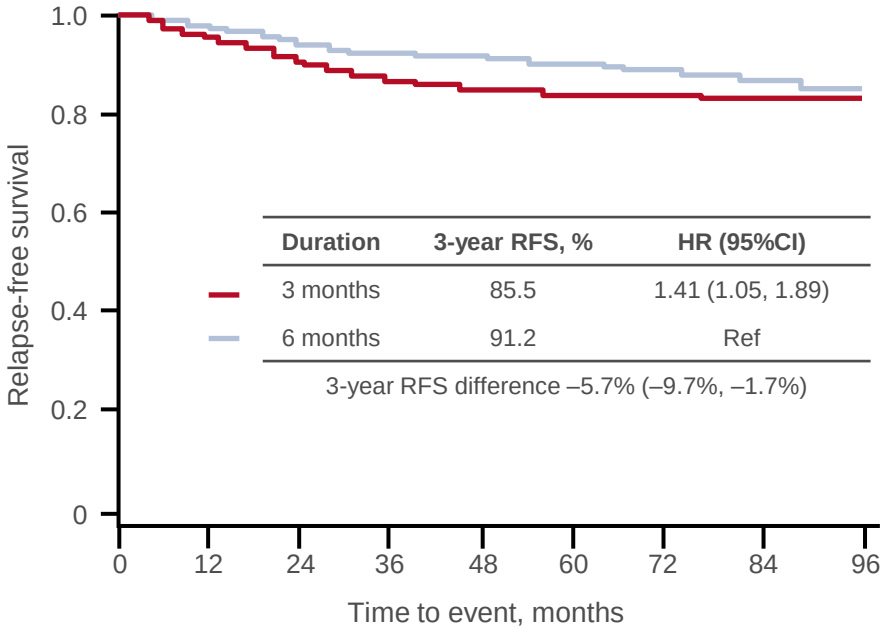
Labianca R, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-025

O-025: FOLFOX4/XELOX in stage II–III colon cancer: Early survival data of the Italian Three Or Six Colon Adjuvant (TOSCA) trial – Labianca R, et al

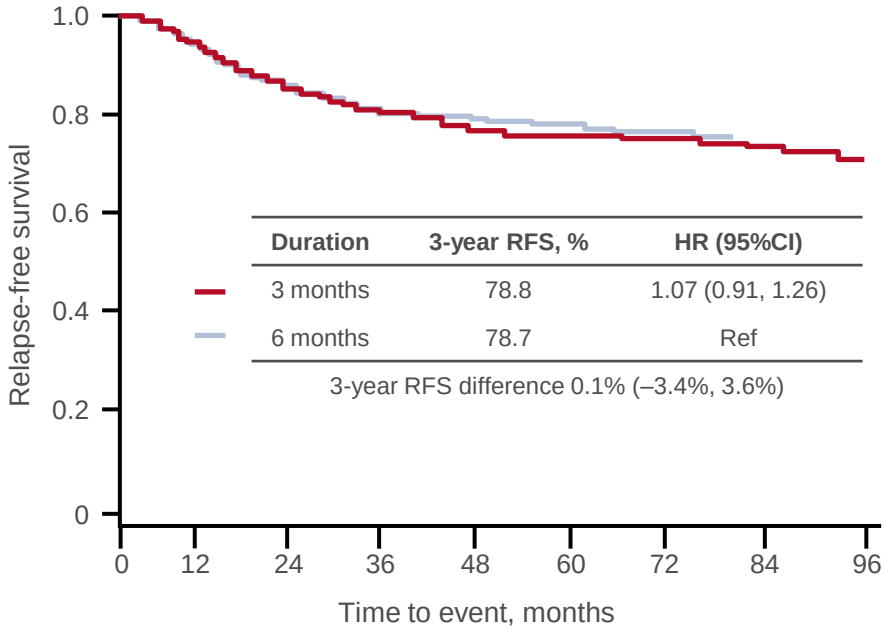
Key results (cont.)

RFS by stage

Stage II



Stage III



Labianca R, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-025

O-025: FOLFOX4/XELOX in stage II–III colon cancer: Early survival data of the Italian Three Or Six Colon Adjuvant (TOSCA) trial – Labianca R, et al

Conclusions

- **This non-inferiority study found that 3 months was not as effective as 6 months for the adjuvant treatment of colon cancer**
- **However, toxicity was significantly improved by the shorter exposure**
- **As the absolute difference between the treatment durations is small (below 3% at 5 years), treatment should be individualised for each patient to consider toxicity and attitude towards therapy**

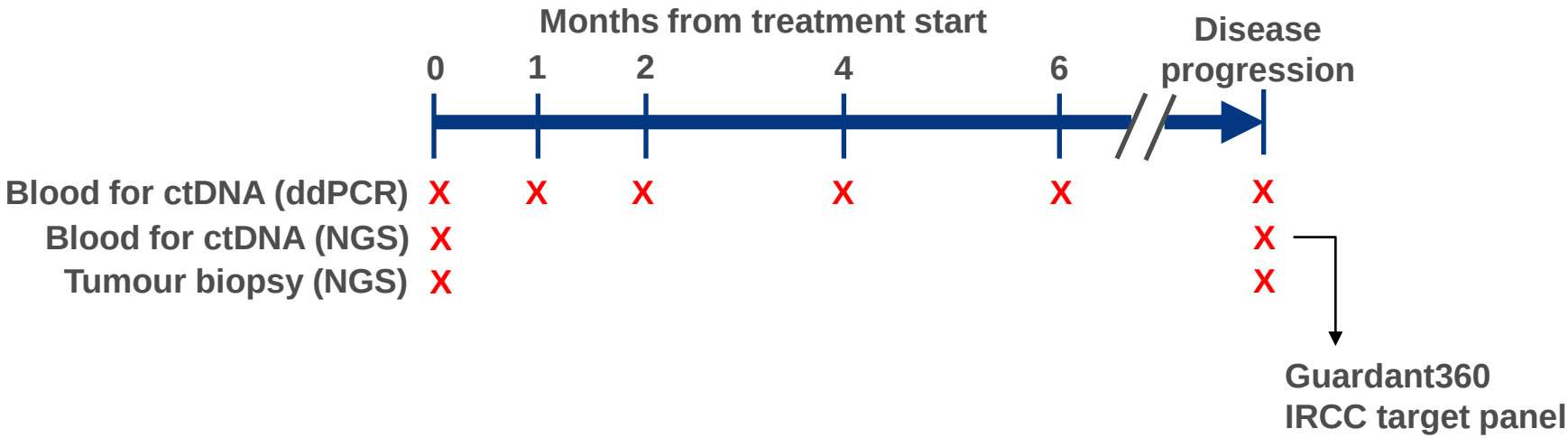
Labianca R, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-025

GASTROINTESTINAL CANCERS

O-001: Systematic liquid biopsy identifies novel and heterogeneous mechanisms of acquired resistance in gastrointestinal (GI) cancer patients – Parikh A, et al

Study objective

- To investigate molecular heterogeneity and resistance mechanisms of different GI tumours by analysing liquid biopsies



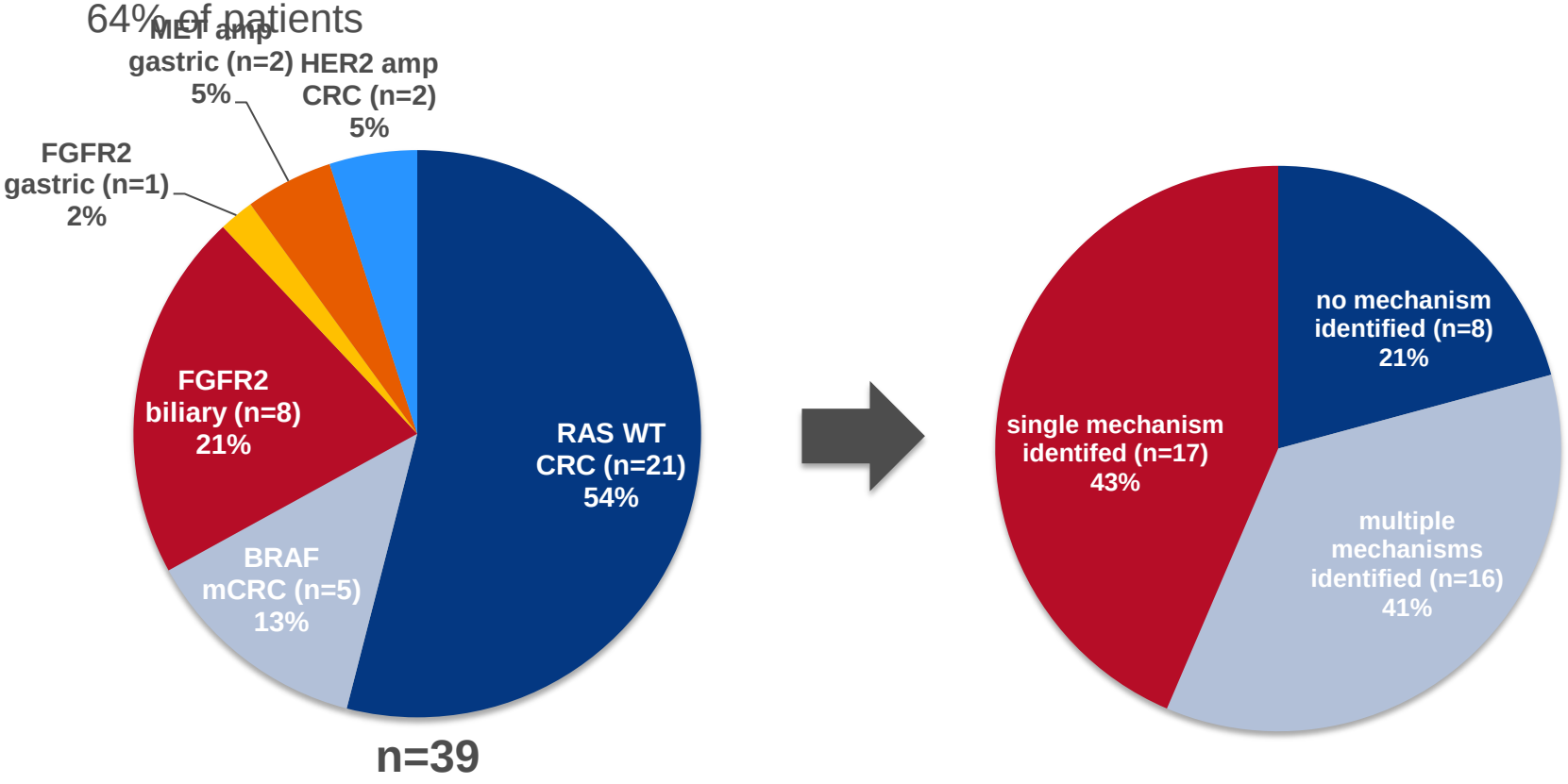
- Liquid biopsy may detect alterations in ctDNA shed by tumour cells throughout the body

Parikh A, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-001

O-001: Systematic liquid biopsy identifies novel and heterogeneous mechanisms of acquired resistance in gastrointestinal (GI) cancer patients – Parikh A, et al

Key results

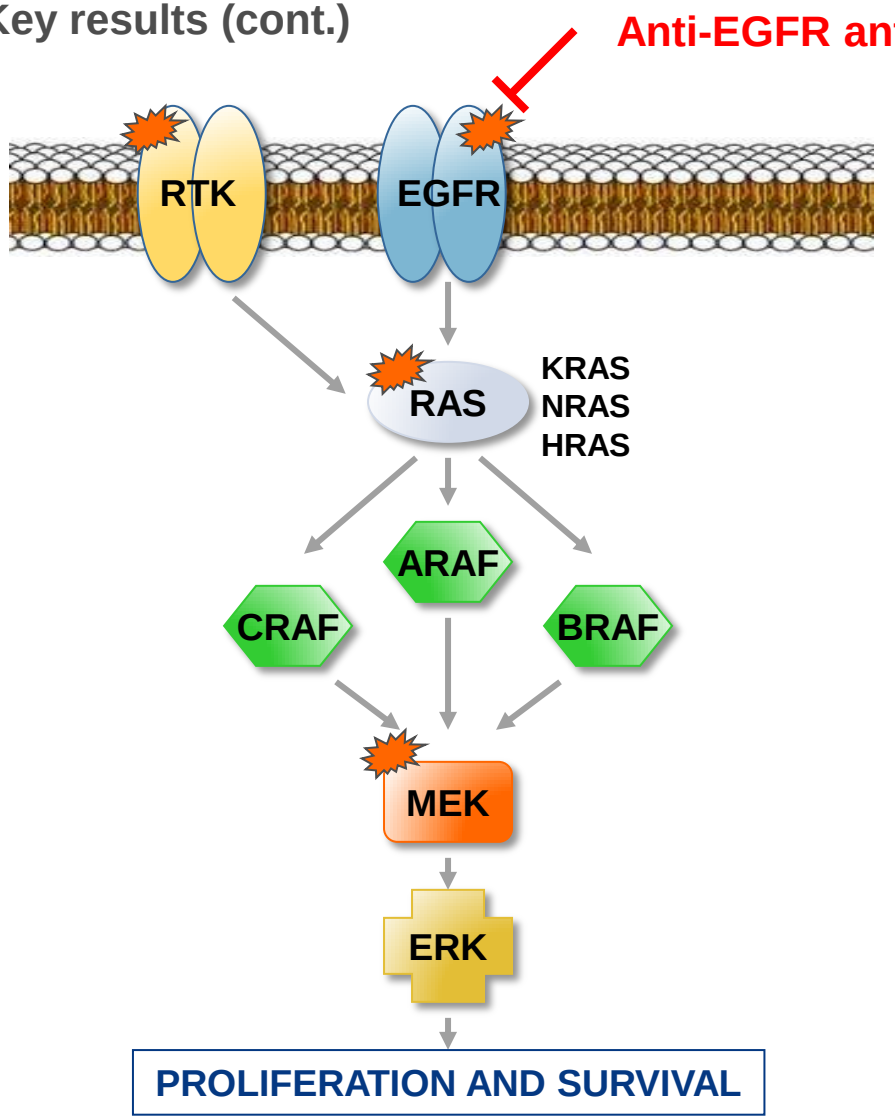
- Mechanism of resistance was identified by liquid biopsy in 80% of patients
- Multiple resistance mechanisms were observed in 41% of patients
- Additional resistance mechanisms were identified by ctDNA in matched tumour biopsies in 64% of patients



Parikh A, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-001

O-001: Systematic liquid biopsy identifies novel and heterogeneous mechanisms of acquired resistance in gastrointestinal (GI) cancer patients – Parikh A, et al

Key results (cont.)



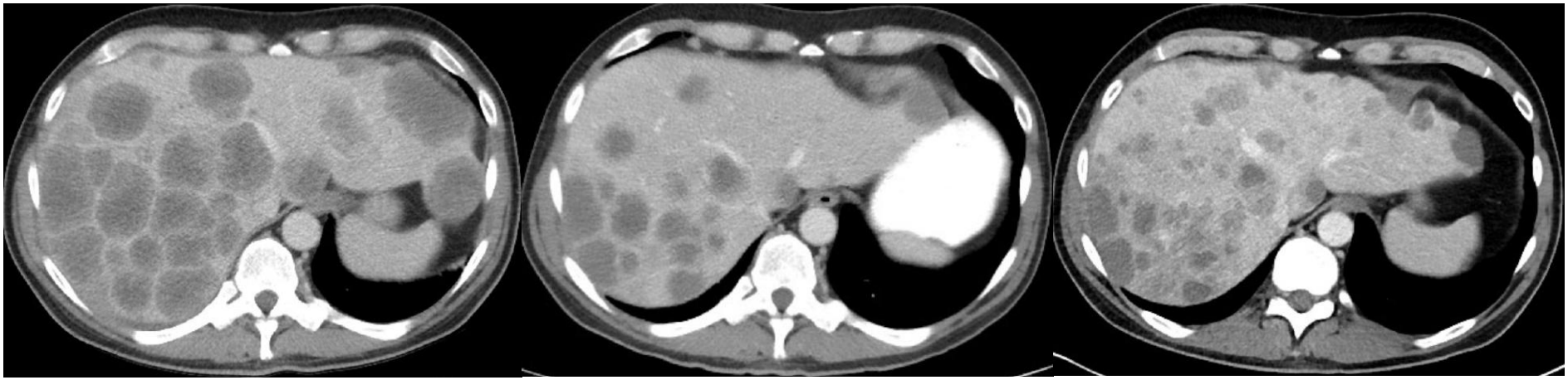
- 10 distinct resistance alterations identified across 21 patients
  - KRAS mutations
  - KRAS amplification
  - EGFR ECD mutations
  - MET amplification
  - ERBB2 amplification
  - Novel MEK1 mutation
- Some patients with 5 or more alterations present in ctDNA

Parikh A, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-001

O-001: Systematic liquid biopsy identifies novel and heterogeneous mechanisms of acquired resistance in gastrointestinal (GI) cancer patients – Parikh A, et al

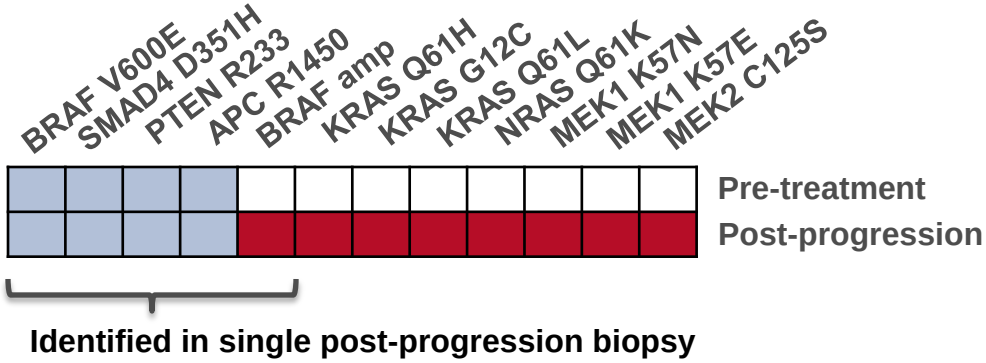
Key results (cont.)

BRAF mutant CRC, dabrafenib, trametinib, panitumumab



Pre-treatment | Response | Progression

(Patient of Jill Allen)



"Founder" mutations present in initial biopsy

Resistance mutations detected at progression

Parikh A, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-001

O-001: Systematic liquid biopsy identifies novel and heterogeneous mechanisms of acquired resistance in gastrointestinal (GI) cancer patients – Parikh A, et al

Conclusions

- **Analysis of liquid biopsies was used to identify:**
  - **Resistance mechanisms across different tumour types and treatments, including several novel ones**
  - **Multiple resistance mechanisms occurring simultaneously**
  - **Resistance mechanisms that had not been identified by tumour biopsy**
- **Liquid biopsies may capture heterogeneity of resistance that single needle biopsies may fail to detect**
- **There may be a role for including liquid biopsy in clinical decision making to help to overcome the heterogeneity of resistance**

Parikh A, et al. Ann Oncol 2017; 28 (suppl 3): abstr O-001