GI SLIDE DECK 2014

Selected abstracts from:

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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 gastric cancers from the major congresses in 2014. This slide set specifically focuses on the American Society of Clinical Oncology Gastrointestinal Cancers Symposium and 50th Annual Meeting.

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

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

Yours sincerely,

Eric Van Cutsem
Wolff Schmiegel
Phillippe Rougier
Thomas Seufferlein
Thomas Grünberger
Jean-Luc Van Laetham
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esdo

european society of digestive oncology

ESDO Medical Oncology Slide Deck Editors 2014



Colorectal cancers

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Biomarkers

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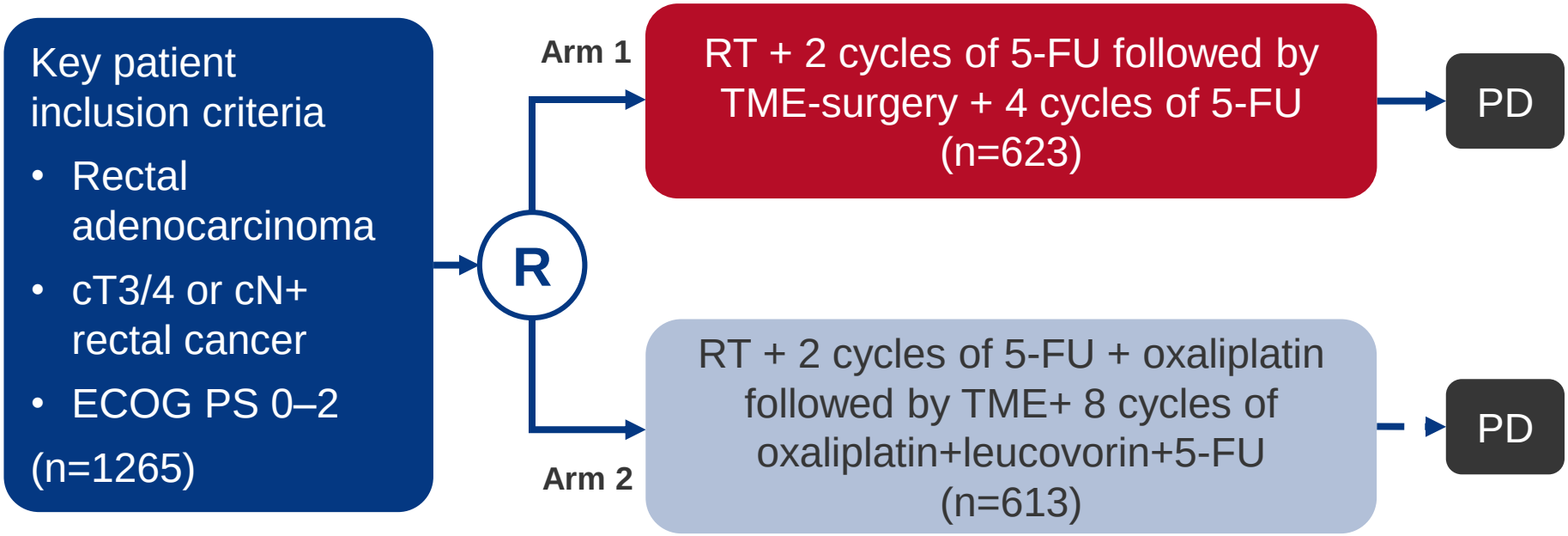
COLORECTAL CANCER

RECTAL CANCER

PERIOPERATIVE TREATMENT

3500: Preoperative chemoradiotherapy and postoperative chemotherapy with 5-fluorouracil and oxaliplatin versus 5-fluorouracil alone in locally advanced rectal cancer: Results of the German CAO/ARO/AIO-04 randomized phase III trial – Rodel C et al

- **Study objective**
  - To assess whether an integrated and more effective systemic treatment in patients with locally advanced rectal cancer improves survival



Primary endpoint

- DFS at 3 years

Secondary endpoints

- Toxicity, tumour response, recurrence and OS

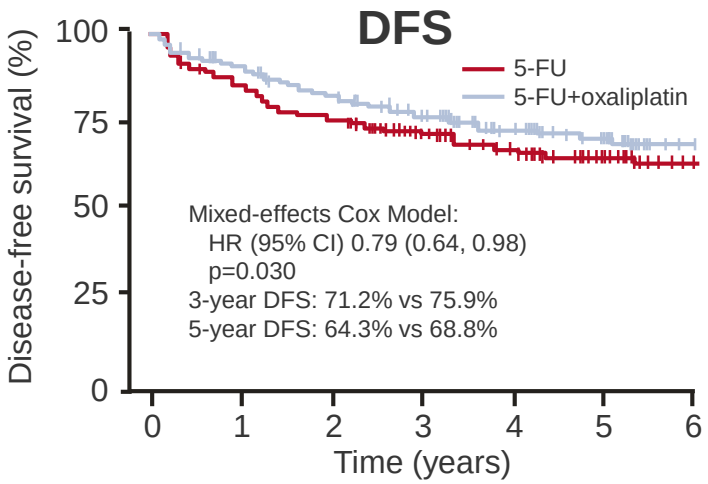
RT, radiotherapy of 50.4 Gy

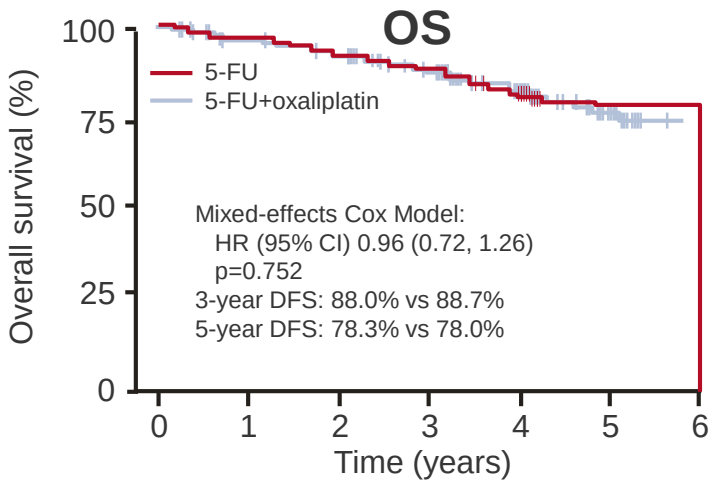
Rodel et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3500)

3500: Preoperative chemoradiotherapy and postoperative chemotherapy with 5-fluorouracil and oxaliplatin versus 5-fluorouracil alone in locally advanced rectal cancer: Results of the German CAO/ARO/AIO-04 randomized phase III trial – Rodel C et al

- **Key results**

	5-FU (n=637)	5-FU+oxaliplatin (n=628)
	Time from randomisation	
Incomplete local resection (R2)	10	5
Loco-regional recurrence after R0/R1 resection	23	12
Distant metastases/progression	149	115
Death	106	96
First events for DFS	198	159





Rodel et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3500)

3500: Preoperative chemoradiotherapy and postoperative chemotherapy with 5-fluorouracil and oxaliplatin versus 5-fluorouracil alone in locally advanced rectal cancer: Results of the German CAO/ARO/AIO-04 randomized phase III trial – Rodel C et al

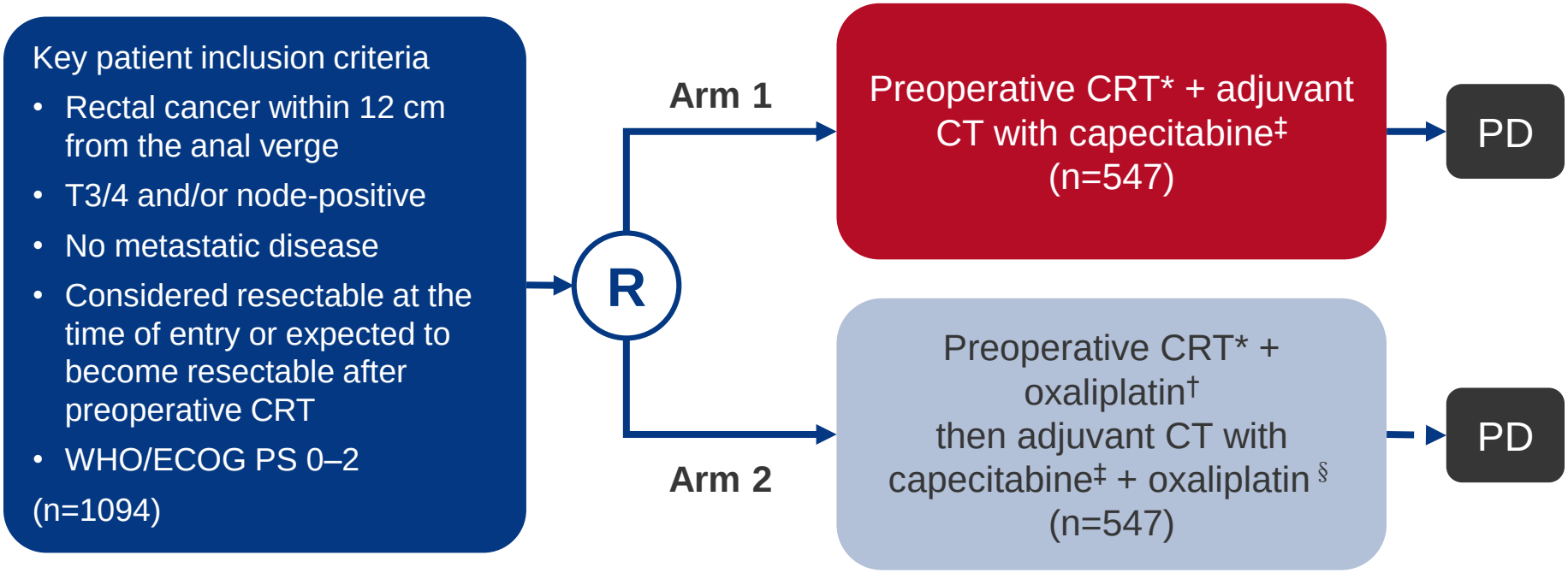
- **Key results**
  - Grade 3–4 late overall treatment-related toxicity:
    - 22% with 5-FU alone vs 26% with 5-FU+oxaliplatin (p=0.14)

- **Conclusions**
  - **Preoperative 5-FU+oxaliplatin CRT was well tolerated, with high compliance and increased pCR rate in locally advanced rectal cancer**
  - **5-FU+oxaliplatin significantly improved DFS compared with 5-FU alone**

Rodel et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3500)

3501: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: Disease-free survival results at interim analysis – Schmoll H-J et al

- **Study objective**
  - To investigate whether the addition of oxaliplatin to preoperative oral fluoropyrimidine-based CRT followed by postoperative adjuvant fluoropyrimidine-based CT improves outcome in locally advanced rectal cancer (PETACC-6 trial)



Primary endpoint

- DFS

Secondary endpoints

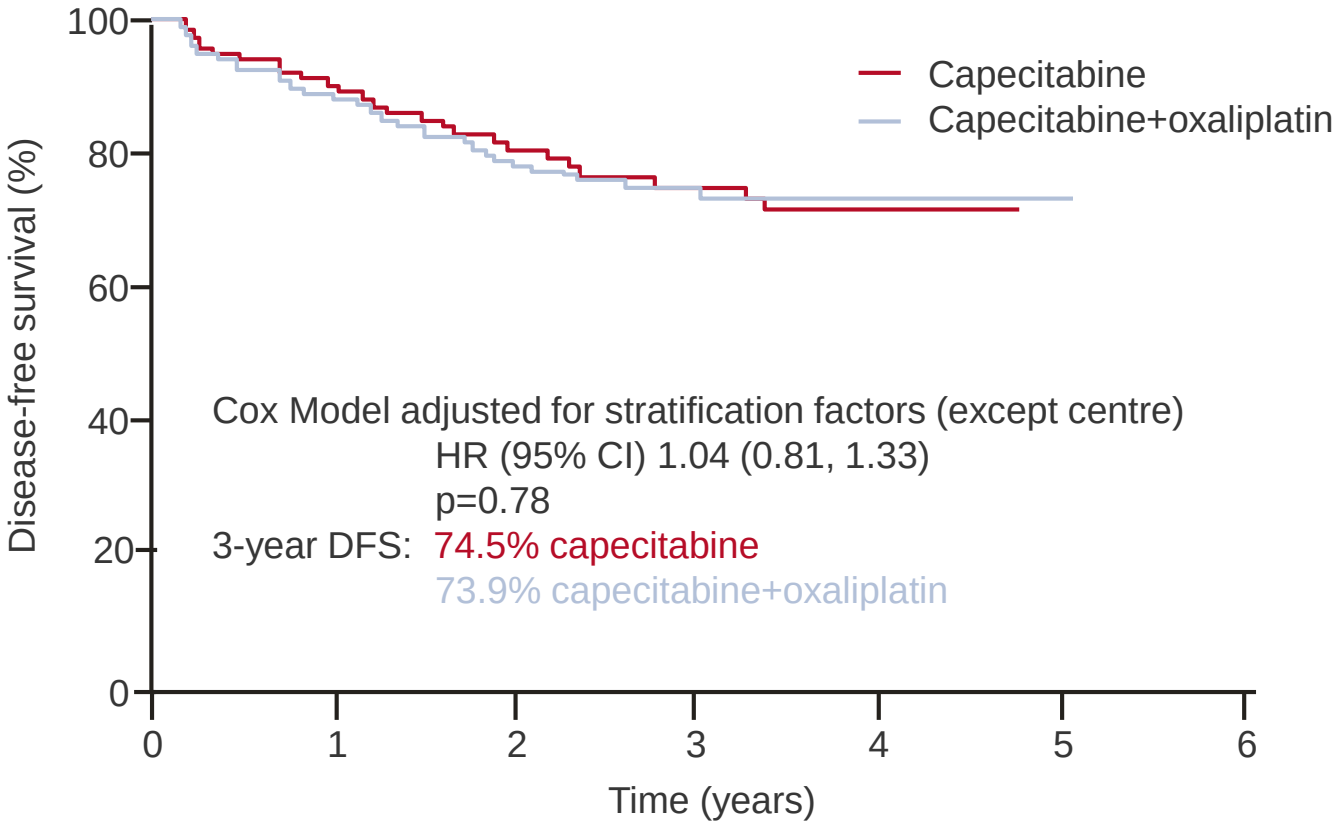
- OS, tumour response

*45 Gy (25 fractions) + capecitabine (825 mg/m² bid) days 1–33 w/o weekends; †50 mg/m² days 1, 8, 15, 22, 29; ‡1000 mg/m² bid days 1–15 q3w (6 cycles); § 130 mg/m² day 1, q3w

Schmoll et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3501)

3501: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: Disease-free survival results at interim analysis – Schmoll H-J et al

- **Key results**
  - At median follow-up of 31 months, 3-year DFS with capecitabine alone was higher than anticipated



Schmoll et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3501)

3501: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: Disease-free survival results at interim analysis – Schmoll H-J et al

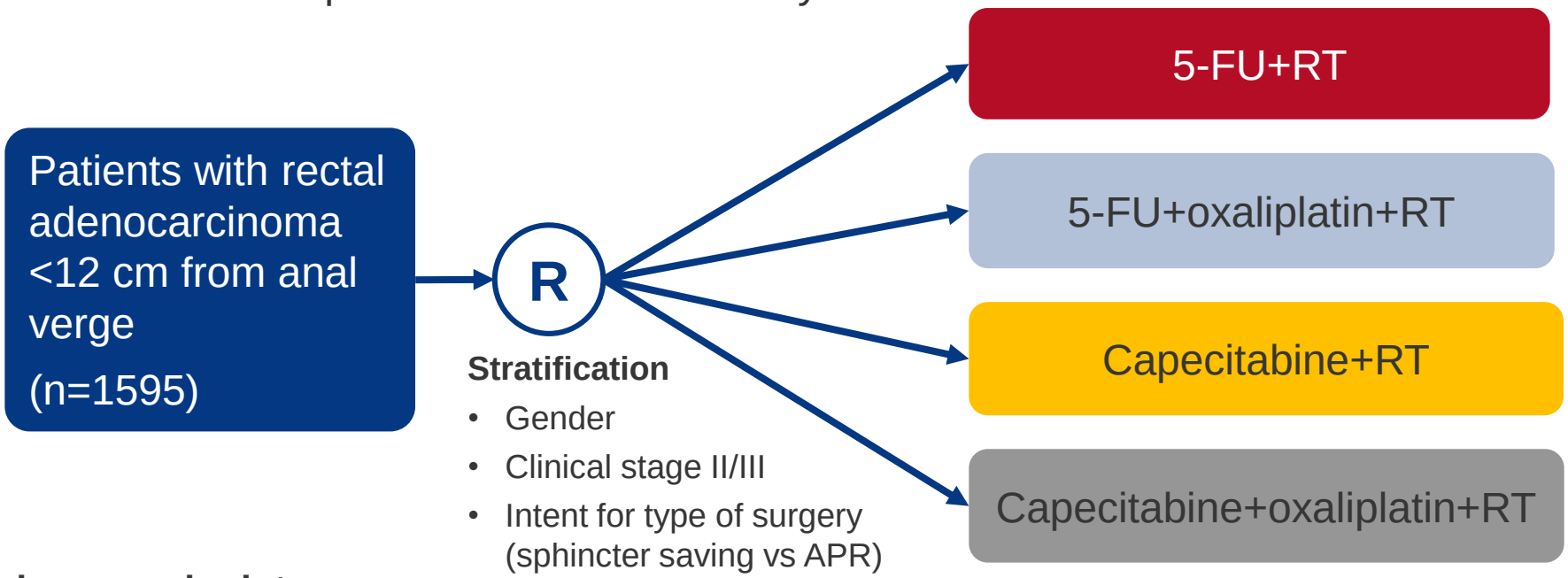
	Capecitabine (n=543)	Capecitabine+ oxaliplatin (n=526)	p-value
Relapse at 3 years, %			
Loco-regional	7.6	4.6	0.094
Distant	19.2	17.6	0.542
OS at 3 years, %	89.5	87.4	0.179
Death without progression, n	15	26	

- **Conclusions**
  - **The addition of oxaliplatin to preoperative capecitabine-based CRT:**
    - **Reduced treatment compliance**
    - **Did not improve R0 resection, pathological CR or sphincter preservation**
  - **The addition of oxaliplatin to pre- and post-operative capecitabine-based CRT did not improve DFS**

Schmoll et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3501)

3603: Final results from NSABP protocol R-04: Neoadjuvant chemoradiation (RT) comparing continuous infusion (CIV) 5-FU with capecitabine (Cape) with or without oxaliplatin (Ox) in patients with stage II and III rectal cancer – Allegra CJ et al

- **Study objective**
  - To evaluate whether capecitabine can be substituted for standard of care (5-FU) in the curative setting of stage II/III rectal cancer during neoadjuvant RT and whether oxaliplatin enhances its activity



Primary endpoint

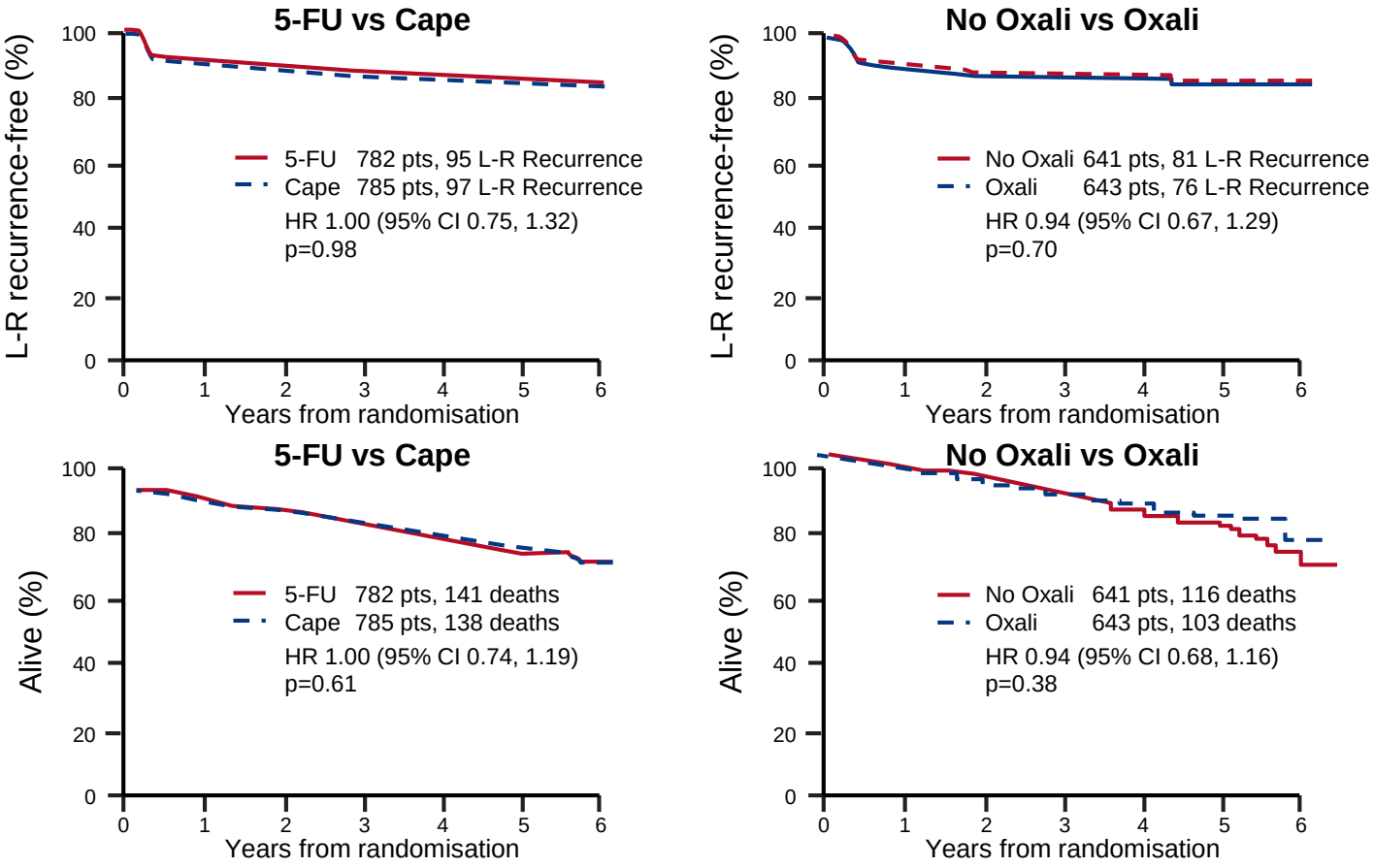
- Local-regional control with 3 years minimum follow-up

5-FU CIVI 225 mg/m^2 5d/wk; RT 46 Gy over 5 wk + boost;
Oxaliplatin 50 mg/m^2/wk x5; Capecitabine 825 mg/m^2 po bid

Allegra et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3603)

3603: Final results from NSABP protocol R-04: Neoadjuvant chemoradiation (RT) comparing continuous infusion (CIV) 5-FU with capecitabine (Cape) with or without oxaliplatin (Ox) in patients with stage II and III rectal cancer – Allegra CJ et al

- **Key results**



  - The addition of oxaliplatin was associated with significantly more overall AEs and grade 3–4 diarrhoea (p<0.0001)

Allegra et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3603)

3603: Final results from NSABP protocol R-04: Neoadjuvant chemoradiation (RT) comparing continuous infusion (CIV) 5-FU with capecitabine (Cape) with or without oxaliplatin (Ox) in patients with stage II and III rectal cancer – Allegra CJ et al

- **Conclusions**
  - **The addition of oxaliplatin did not improve outcomes but led to significant rates of diarrhoea and, therefore, is not recommended to be combined with RT in the preoperative rectal setting**
  - **Capecitabine may be used as standard of care in the preoperative rectal setting**
  - **Molecular studies using this fully annotated tissue bank are ongoing**

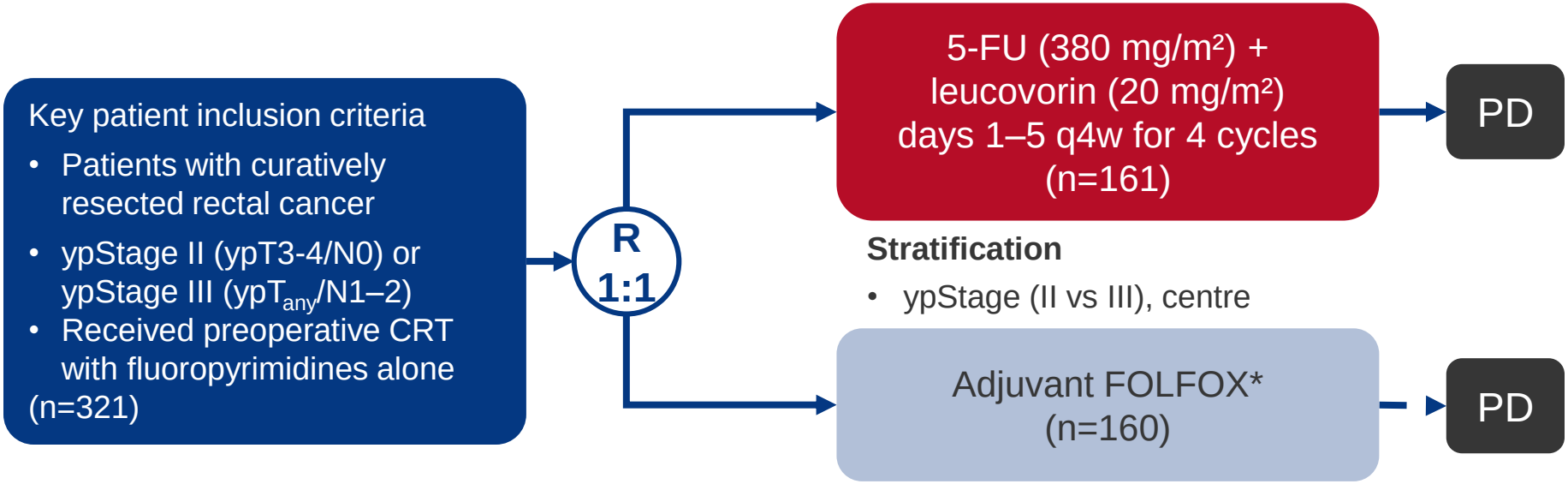
Allegra et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3603)

RECTAL CANCER

ADJUVANT THERAPY

3502: Adjuvant chemotherapy with oxaliplatin/5-fluorouracil/leucovorin (FOLFOX) versus 5-fluorouracil/leucovorin (FL) for rectal cancer patients whose postoperative yp stage 2 or 3 after preoperative chemoradiotherapy: Updated results of 3-year disease-free survival from a randomized phase II study (The ADORE) – Hong YS et al

- **Study objective**
  - To investigate the addition of oxaliplatin (FOLFOX regimen) to 5-FU+leucovorin in patients with resected rectal cancer



Primary endpoint

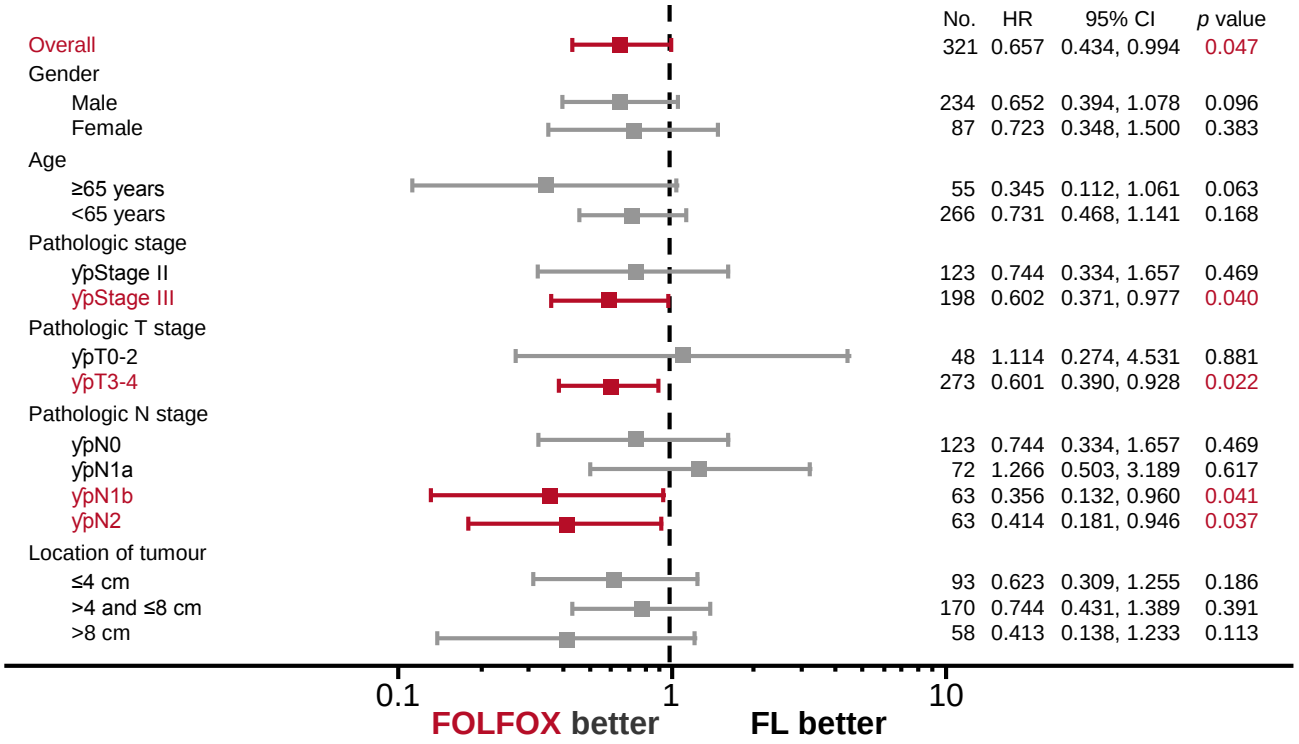
- DFS at 3 years

*oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, 5-FU bolus 400 mg/m^2 on day 1, 5-FU infusion 2400 mg/m^2 for 46 hours q2w for 8 cycles

Hong et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3502)

3502: Adjuvant chemotherapy with oxaliplatin/5-fluorouracil/leucovorin (FOLFOX) versus 5-fluorouracil/leucovorin (FL) for rectal cancer patients whose postoperative yp stage 2 or 3 after preoperative chemoradiotherapy: Updated results of 3-year disease-free survival from a randomized phase II study (The ADORE) – Hong YS et al

- **Key results**
  - At median follow-up of 38.2 months patients benefitted more from FOLFOX than 5-FU+leucovorin



Hong et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3502)

3502: Adjuvant chemotherapy with oxaliplatin/5-fluorouracil/leucovorin (FOLFOX) versus 5-fluorouracil/leucovorin (FL) for rectal cancer patients whose postoperative yp stage 2 or 3 after preoperative chemoradiotherapy: Updated results of 3-year disease-free survival from a randomized phase II study (The ADORE) – Hong YS et al

- **Conclusions**
  - **Adjuvant FOLFOX demonstrated improved 3-year DFS in curatively resected rectal cancer patients whose were postoperative ypStage II/III after preoperative CRT**
  - **Adjuvant FOLFOX remained a significant factor affecting 3-year DFS**

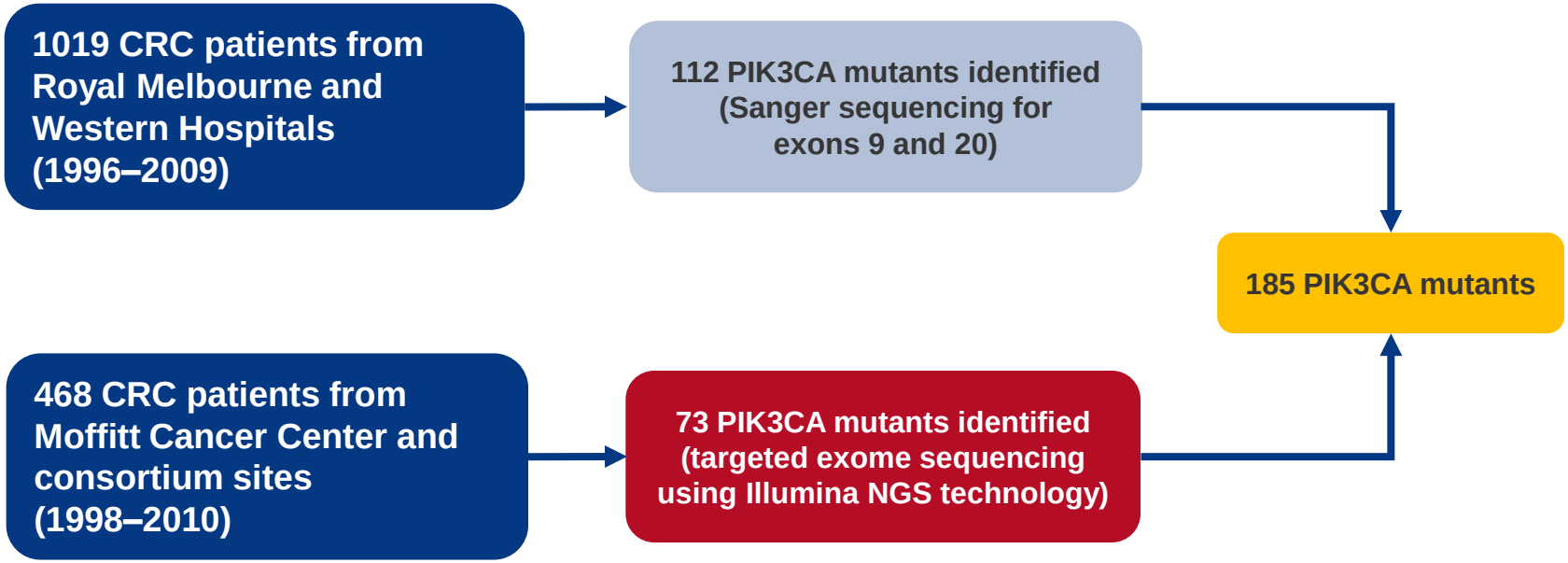
Hong et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3502)

COLON CANCER

ADJUVANT THERAPY

386: Regular aspirin (ASA) use and survival in patients with PIK3CA-mutated metastatic colorectal cancer (CRC) – Kothari N et al

- **Study objective**
  - A retrospective analysis of the benefits on survival of aspirin therapy in CRC and to determine the role of PIK3CA as a predictive biomarker



Primary endpoint

- OS

Kothari et al. J Clin Oncol 2014; 32 (suppl 3; abstr 386)

386: Regular aspirin (ASA) use and survival in patients with PIK3CA-mutated metastatic colorectal cancer (CRC) – Kothari N et al

- **Key results**
  - Of 185 patients identified with PIK3CA mutations, mean age was 72 years, median follow-up was 46 months, 107 had right-sided primary site (77 left sided and 1 unknown) and 8 had AJCC stage 1, 66 stage 2, 67 stage 3 and 44 stage 4

CRC stage	Outcome	HR	95% CI	p-value
All stages Aspirin (n=49) No aspirin (n=136)	OS	0.96	0.58, 1.57	0.86
Stage 2 Aspirin (n=16) No aspirin (n=50)	RFS	1.34	0.22, 5.81	0.67
Stage 3 Aspirin (n=22) No aspirin (n=45)	RFS	0.85	0.30, 2.40	0.76
Stage 4 Aspirin (n=9) No aspirin (n=35)	OS	0.40	0.21, 1.00	0.06

Kothari et al. J Clin Oncol 2014; 32 (suppl 3; abstr 386)

386: Regular aspirin (ASA) use and survival in patients with PIK3CA-mutated metastatic colorectal cancer (CRC) – Kothari N et al

- **Conclusions**
  - **There was no survival benefit associated with aspirin in patients with PIK3CA mutations**
  - **In patients with stage 2 and 3 CRC aspirin was not demonstrated to provide any benefit on recurrence-free survival**
  - **There may be a trend towards survival benefit in patients with stage 4 CRC**

Kothari et al. J Clin Oncol 2014; 32 (suppl 3; abstr 386)

3507: Prognostic impact of deficient mismatch repair (dMMR) in 7,803 stage II/III colon cancer (CC) patients (pts): A pooled individual pt data analysis of 17 adjuvant trials in the ACCENT database – Sargent DJ et al

- **Study objective**
  - To investigate the prognostic effect of mismatch repair of proteins MLH1, MSH2 and MLH6 in patients with stage II/III colon cancer
- **Study design**
  - Retrospective study analysing data for 7803 patients from 17 trials
    - Patients were treated with 5-FU monotherapy, 5-FU+oxaliplatin, 5-FU+irinotecan or surgery alone
  - Tumours with MSI-high or an absent protein were classified as dMMR; remainder were pMMR
  - Primary endpoints: TTR, OS
  - All analyses were stratified by study arm
  - Median follow-up 7 years

dMMR, deficient mismatch repair; MSI, microsatellite instability; pMMR, MMR-proficient

Sargent et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3507)

3507: Prognostic impact of deficient mismatch repair (dMMR) in 7,803 stage II/III colon cancer (CC) patients (pts): A pooled individual pt data analysis of 17 adjuvant trials in the ACCENT database – Sargent DJ et al

- **Key results**
  - Compared with pMMR, dMMR was associated with improved survival (table)

	5-year TTR				5-year OS			
	Recurrence-free (%)		HR	p	Recurrence-free (%)		HR	p
Treatment	dMMR	pMMR			dMMR	pMMR		
Stage II								
Surgery alone (n=307)	89	74	0.35 (0.15, 0.80)	0.013	90	78	0.37 (0.17, 0.81)	0.013
5-FU-mrx (n=1155)	88	83	0.84 (0.57, 1.24)	0.37	88	87	0.91 (0.63, 1.31)	0.62
Stage III								
Surgery alone (n=264)	60	47	0.79 (0.45, 1.39)	0.41	59	54	0.84 (0.49, 1.43)	0.51
5-FU-mrx (n=2723)	72	64	0.82 (0.67, 0.99)	0.040	77	71	0.81 (0.67, 0.99)	0.039

Sargent et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3507)

3507: Prognostic impact of deficient mismatch repair (dMMR) in 7,803 stage II/III colon cancer (CC) patients (pts): A pooled individual pt data analysis of 17 adjuvant trials in the ACCENT database – Sargent DJ et al

- **Key results**

Multivariate analysis (untreated patients)	TTR		OS	
Markers	**HR**	**p**	**HR**	**p**
Stage (III vs II)	**3.05**	**<0.001**	**2.75**	**<0.001**
Age, 5 years increase	**0.95**	**0.11**	**1.02**	**0.54**
Gender (male vs female)	**1.31**	**0.09**	**1.18**	**0.29**
Tumor location (right vs left)	**0.74**	**0.06**	**0.88**	**0.42**
T-stage				
T3 vs T2	**3.13**	**0.05**	**2.43**	**0.09**
T4 vs T2	**7.29**	**0.02**	**5.22**	**0.004**
MMR (dMMR vs pMMR)	**0.46**	**0.01**	**0.50**	**0.02**

- **Conclusions**
  - **MMR status was associated with younger, female patients; N0; T3/4; right sided**
  - **MMR did not impact post-recurrence survival**
  - **MMR is a prognostic marker in untreated stage II and III patients**
  - **MMR is also prognostic in 5-FU, but with reduced impact**
  - **Stage II dMMR patients should not be recommended for treatment due to their excellent prognosis (~90% 5-year OS)**

Sargent et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3507)

3508: Impact of adjuvant chemotherapy with 5-FU or FOLFOX in colon cancers with microsatellite instability: An AGEO multicenter study – Tougeron D et al

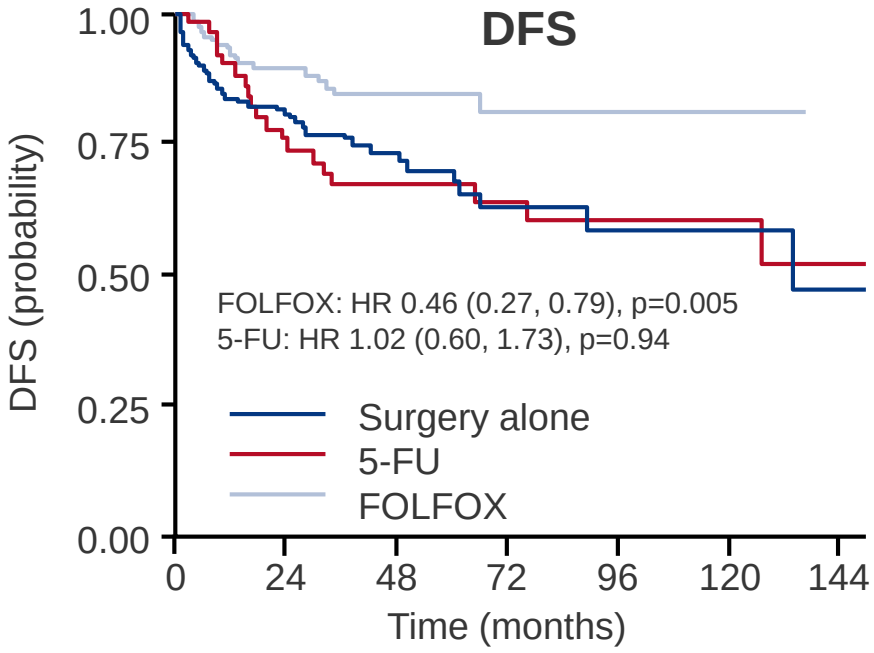
- **Study objective**
  - To identify predictive factors of recurrence and analyse the efficacy of adjuvant CT with 5-FU or FOLFOX vs surgery alone in patients with MSI-H colon cancer
- **Study design**
  - Retrospective study of 528 patients with stage I, II or III MSI-H CRC who had undergone curative surgery between 2000 and 2011
  - High-risk stage II colon cancers were defined by one of these criteria: stage T4, bowel obstruction, tumour perforation, vascular emboli, lymphatic invasion, perinervous invasion or a number of lymph nodes examined inferior to 10
  - Prognostic factors of RFS were analysed in univariate and multivariate analysis using Cox model

MSI, microsatellite instability; RFS, relapse-free survival

Tougeron et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3508)

3508: Impact of adjuvant chemotherapy with 5-FU or FOLFOX in colon cancers with microsatellite instability: An AGEO multicenter study – Tougeron D et al

- **Key results**
  - 3-year DFS: 76% (stage II: 2/6%, stage III: 15/23% with/without CT, respectively)



3-year DFS:
- Surgery alone 75%
- 5-FU 66%
- FOLFOX 84%

(p=0.02)

  - Multivariate analysis of DFS with CT vs surgery alone:
    - 5-FU: HR (95% CI) 0.84 (0.37, 1.92), p=0.68
    - FOLFOX: HR (95% CI) 0.40 (0.20, 0.79), p=0.009

Tougeron et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3508)

3508: Impact of adjuvant chemotherapy with 5-FU or FOLFOX in colon cancers with microsatellite instability: An AGEO multicenter study – Tougeron D et al

- **Key results**
  - Subgroup analysis analysing survival by TNM stage or MSI mechanism:

Survival	FOLFOX			5-FU		
	HR	95% CI	p	HR	95% CI	p
TNM stage						
Stage III (n=187)	0.32	0.17, 0.62	<0.001	0.70	0.37, 1.34	0.28
High-risk stage II (n=149)	0.13	0.02, 0.98	0.05	0.55	0.13, 2.35	0.41
MSI mechanism						
Sporadic (n=274)	0.55	0.29, 1.04	0.07	0.83	0.41, 1.71	0.62
Lynch syndrome (n=125)	0.56	0.19, 1.67	0.30	1.43	0.52, 3.96	0.49

- **Conclusions**
  - **In contrast to 5-FU, patients with stage III MSI-H CRC benefit from adjuvant CT with FOLFOX, with a trend for high-risk stage II**
  - **There was no impact of MSI-H mechanism (sporadic vs Lynch syndrome)**
  - **Further studies are now needed to confirm these results**

Tougeron et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3508)

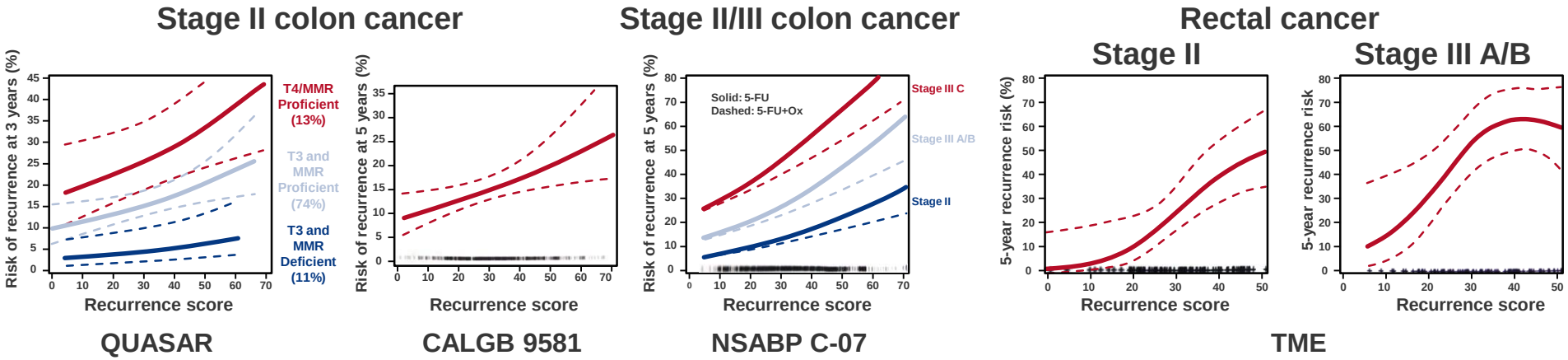
3547: The 12-gene colon cancer assay validation and utility: Summary of clinical evidence – Burke E et al

- **Study objective**
  - To validate the 12-gene colon cancer assay as a reliable molecular assay to predict the risk of recurrence in stage II/III CRC
- **Study design**
  - Analysis of archived tissue from multiple large, prospectively designed studies with pre-specified methods, clinical outcomes and analysis plan
  - Data from four independent studies were analysed comprising 3315 patients:
    - QUASAR study, stage II colon cancer (n=1436)
    - CALGB 9581 study, stage II colon cancer (n=690)
    - NSABP study, stage II/III colon cancer (n=892)
    - TME trial, stage II/III rectal cancer (n=297)

Burke et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3547)

3547: The 12-gene colon cancer assay validation and utility: Summary of clinical evidence – Burke E et al

- **Key results**
  - There was a significant association ($p<0.05$) between the assay result and outcome (e.g. recurrence risk: see figures) in all four studies



- **Conclusions**
  - **The 12-gene colon assay predicts the risk of recurrence**
  - **The test may allow clinicians and patients to make more informed decisions regarding adjuvant CT, which may maximise treatment benefits while minimising unnecessary exposure to toxic agents**

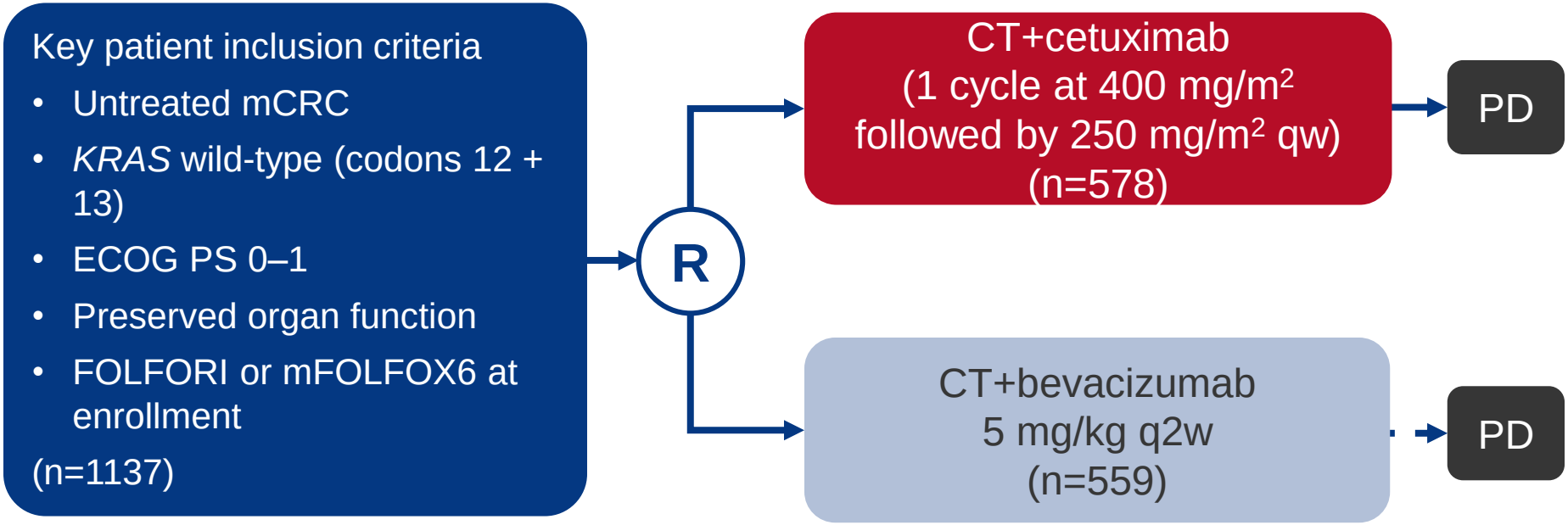
Burke et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3547)

COLORECTAL CANCER

PALLIATIVE / METASTATIC

LBA3: CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC) – Venook AP et al

- **Study objective**
  - To investigate the optimal combination of first-line CT treatment in patients with metastatic adenocarcinoma of the colon or rectum



Primary endpoint

- OS

Secondary endpoints

- PFS and CT/biological interactions

Venook et al. J Clin Oncol 2014; 32 (suppl 5; abstr LBA3)

LBA3: CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC) – Venook AP et al

- **Key results**

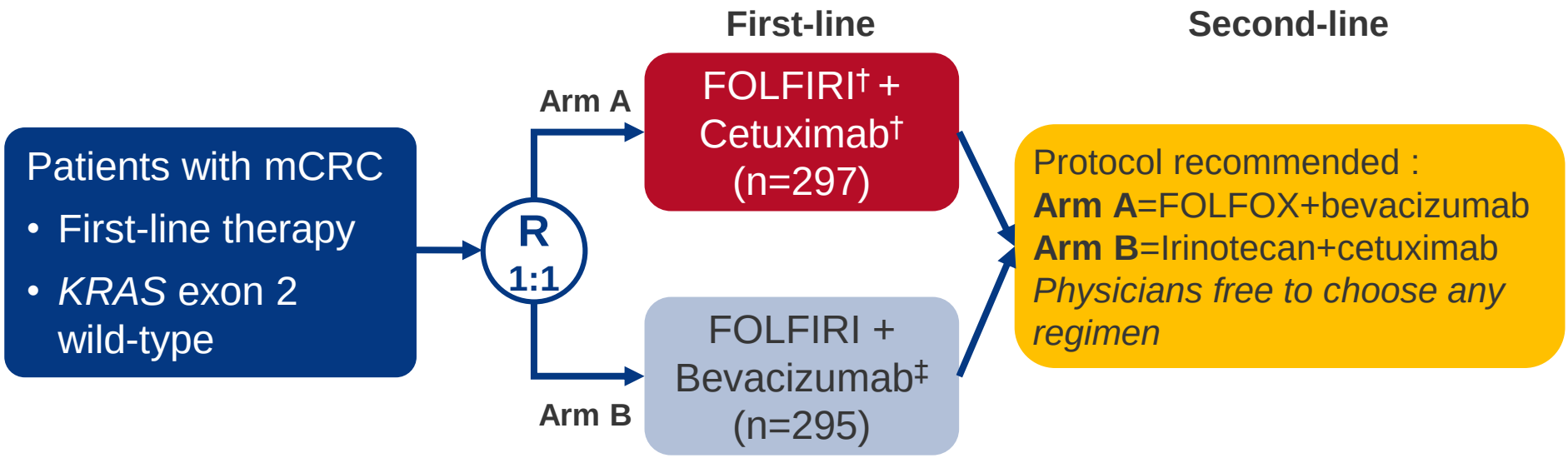
	N	OS (mo)	HR	CI	p
CT+cetuximab	**578**	**29.9**	**0.92**	**0.78, 1.09**	**0.34**
CT+bevacizumab	**559**	**29.0**			
FOLFOX+cetuximab	426	30.1	0.9	0.7, 1.0	0.09
FOLFOX+bevacizumab	409	26.9			
FOLFIRI+cetuximab	152	28.9	1.2	0.9, 1.6	0.28
FOLFIRI+bevacizumab	150	33.4			

  - Patients rendered disease-free (n=124): median OS 66.3 (95% CI 59.8, n/a) mo
  - Grade 3/4 toxicity: bevacizumab 52%/12.4%; cetuximab 54%/13.7%
- **Conclusions**
  - **OS with CT+cetuximab was no different from CT+bevacizumab**
  - **FOLFIRI or FOLFOX with either bevacizumab or cetuximab is an appropriate first-line treatment for patients with *KRAS* wild-type mCRC**
  - ***RAS* analysis not yet available**

Venook et al. J Clin Oncol 2014; 32 (suppl 5; abstr LBA3)

3558: Second-line therapies in patients with *KRAS* wild-type metastatic colorectal cancer (mCRC) after first-line therapy with FOLFIRI in combination with cetuximab or bevacizumab in the AIO KRK0306 (FIRE 3) trial – Modest DP et al

- **Study objective**
  - To investigate the choice, duration and outcome of second-line therapies in patients with *KRAS* exon 2 wild-type mCRC



Primary endpoint

- Overall response rate

Secondary endpoints

- PFS and OS

*5-FU 400 mg/m^2 iv bolus + 2400 mg/m^2 iv 46 h, folinic acid 400 mg/m^2, irinotecan 180 mg/m^2; †cetuximab 400 mg/m^2 iv 120 min initial dose + 250 mg/m^2 iv 60 min q1w; ‡bevacizumab 5 mg/kg iv 30–90 min q2w

Modest et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3558)

3558: Second-line therapies in patients with *KRAS* wild-type metastatic colorectal cancer (mCRC) after first-line therapy with FOLFIRI in combination with cetuximab or bevacizumab in the AIO KRK0306 (FIRE 3) trial – Modest DP et al

- **Key results**

	CT+cetuximab	CT+bevacizumab	p
Overall response rate, %	62	58	0.183
PFS, months	10.0	10.3	0.547
OS, months	28.7	25.0	0.017

Survival according to 2nd-line mAB use, mo	*CT+cetuximab			p‡	*CT+bevacizumab			p‡
	†EGFR	†VEGF	†None		†EGFR	†VEGF	†None	
PFS of 1st-line therapy	9.7	9.7	11.4	0.03	9.7	10.1	11.3	<0.001
OS of 1st-line therapy	33.5	23.7	38.3	0.25	21.8	30.8	28.4	0.01
OS of 2nd-line therapy	17.3	15.3	20.2	0.58	10.5	17.5	15.3	0.07

- **Conclusions**
  - **Patients with favourable first-line PFS were more likely to be treated with no mAB as second-line treatment**
  - **There was, therefore, a trend towards more favourable OS and second-line OS in patients receiving no second-line mAB therapy**
  - **There was a trend towards longer second-line therapy in the cetuximab arm**

*First-line therapy; †second-line mAB therapy; ‡log-rank

Modest et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3558)

3550: Survival outcomes in patients (pts) with *KRAS*/*NRAS* (*RAS*) wild-type (WT) metastatic colorectal cancer (mCRC) and non-liver-limited disease (non-LLD): Data from the PRIME study – Douillard J-Y et al

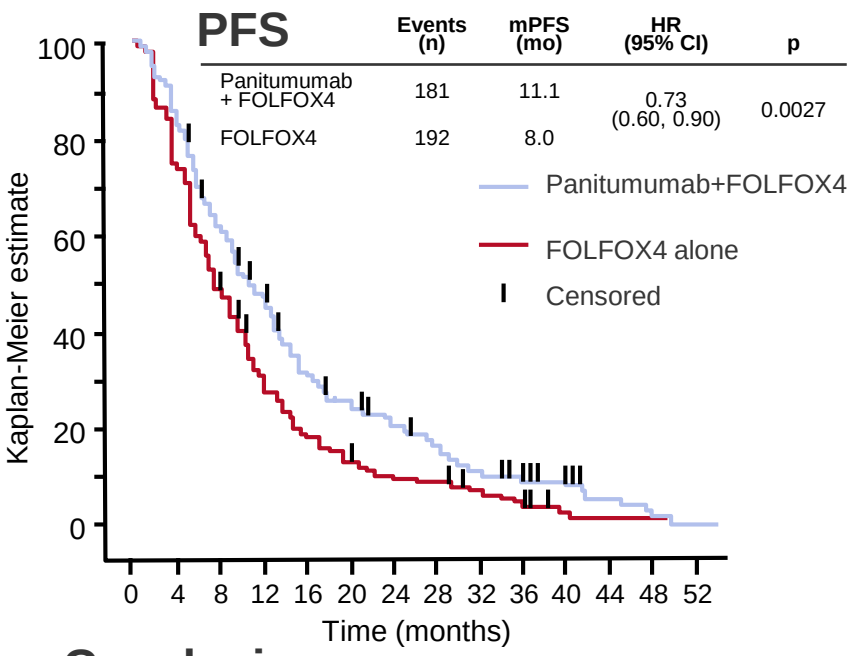
- **Study objective**
  - To assess the efficacy of panitumumab+FOLFOX4 vs FOLFOX4 alone in patients with *RAS* wild-type mCRC whose metastases were not limited to the liver (non-LLD)
- **Study design**
  - *Post-hoc* analysis of the randomised phase III PRIME study, which evaluated panitumumab with FOLFOX4 as first-line therapy in patients with mCRC
    - Patients were randomly allocated (1:1) to panitumumab 6.0 mg/kg q2w + FOLFOX4 or FOLFOX4 alone and had no prior chemotherapy for mCRC, ECOG PS ≤2 and tumour tissue for biomarker testing
  - Exploratory analysis were conducted when ≥80% of patients had an OS event, median PFS and OS were estimated for patients with *RAS* wild-type mCRC (*KRAS/NRAS* exons 2–4 assessed, including codon 59) and non-LLD
  - 3-year PFS and OS rates were also evaluated

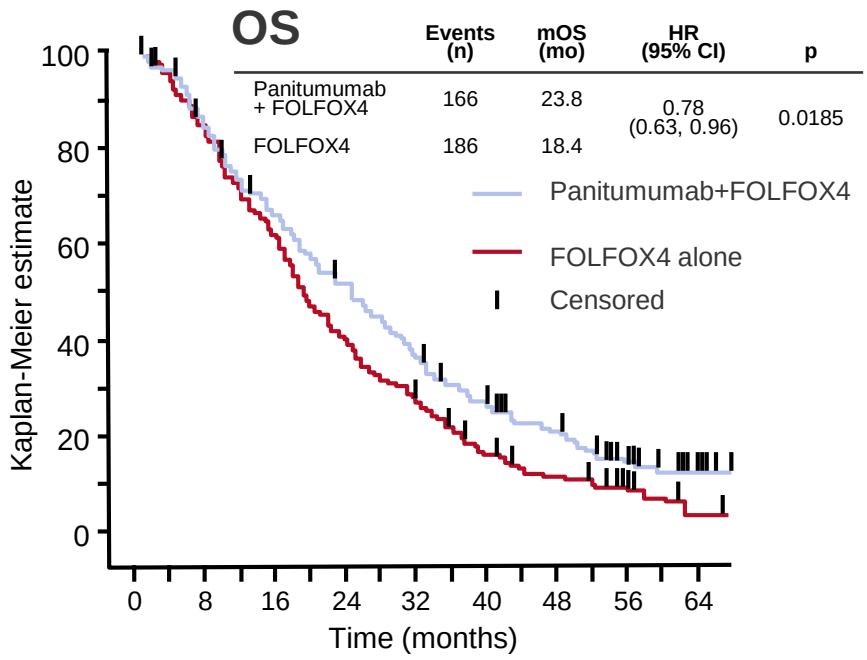
Non-LLD, metastases not limited to the liver

Douillard et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3550)

3550: Survival outcomes in patients (pts) with *KRAS*/*NRAS* (*RAS*) wild-type (WT) metastatic colorectal cancer (mCRC) and non-liver-limited disease (non-LLD): Data from the PRIME study – Douillard J-Y et al

- **Key results**
  - mPFS/OS were longer in patients receiving panitumumab+FOLFOX4 vs FOLFOX4





- **Conclusion**
  - **The PFS and OS benefits observed with 1st-line panitumumab+FOLFOX4 vs FOLFOX4 alone in the overall PRIME population are also seen in the subgroup of patients who have non-LLD**

Douillard et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3550)

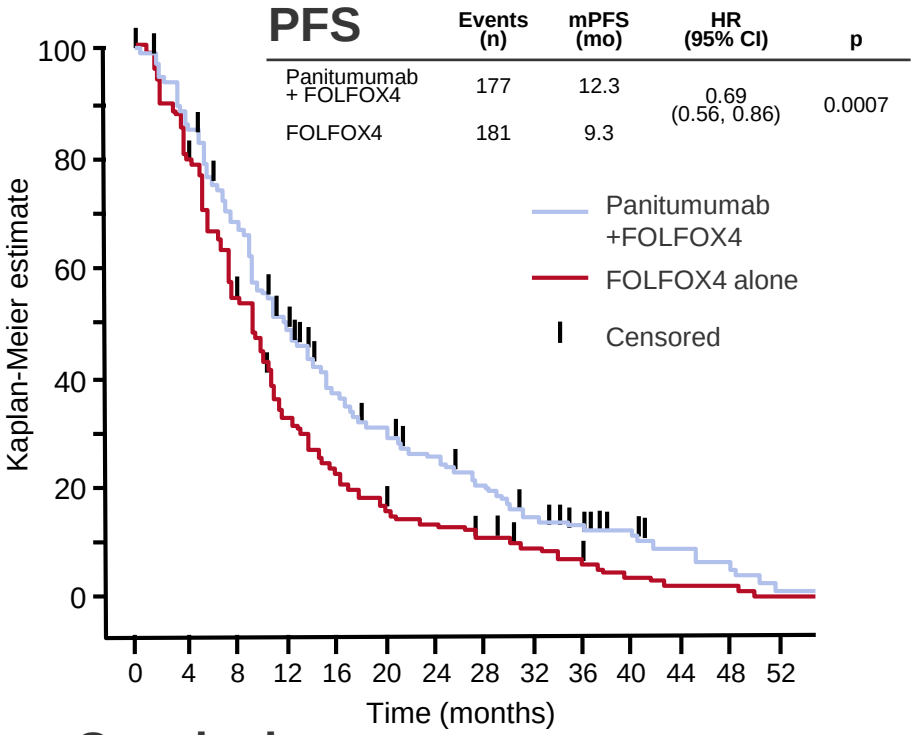
3557: Survival outcomes in the PRIME study for patients (pts) with *RAS*/*BRAF* wild-type (WT) metastatic colorectal cancer (mCRC), by baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) – Peeters M et al

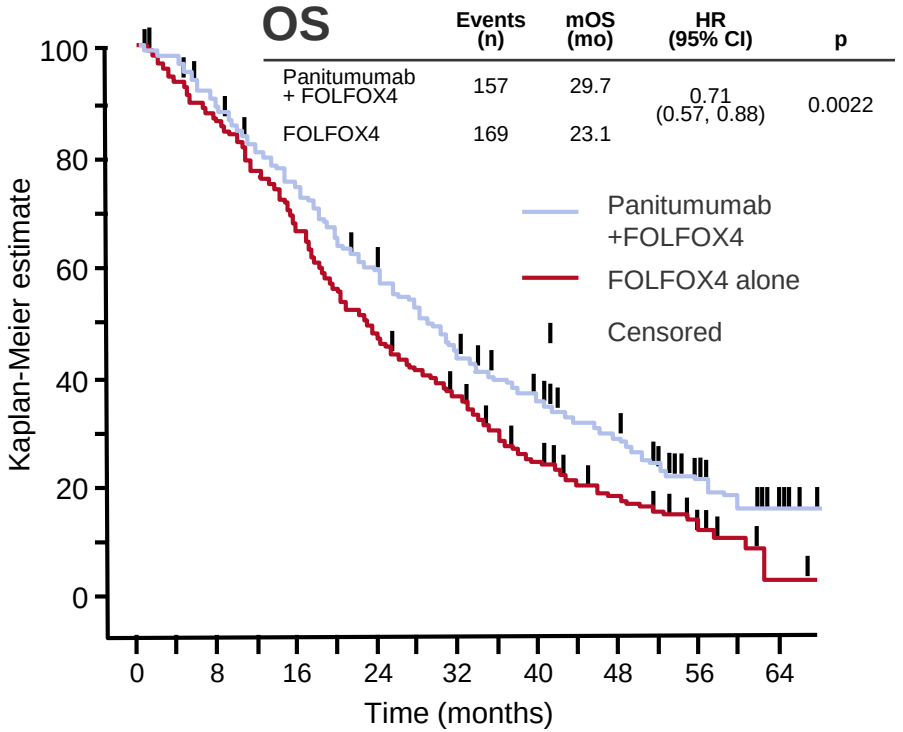
- **Study objective**
  - To estimate treatment effect of panitumumab+FOLFOX4 vs FOLFOX4 alone on OS in patients with *RAS/BRAF* wild-type mCRC by baseline ECOG status
- **Study design**
  - *Post-hoc* analysis of the randomised phase III PRIME study, which evaluated panitumumab+FOLFOX4 as first-line treatment in patients with mCRC
    - Patients were randomly allocated to panitumumab 6.0 mg/kg q2w + FOLFOX4 or FOLFOX4 alone and had no prior chemotherapy for mCRC, ECOG PS ≤2 and tumour tissue for biomarker testing
  - Exploratory analysis was conducted when ≥80% of patients had an OS event, median PFS and OS were estimated for patients with *RAS/BRAF* wild-type mCRC, tested for *NRAS* exon 2 (codons 12/13), *KRAS/NRAS* exon 3 (codons 59/61) and exon 4 (codons 117/146) and *BRAF* exon 15 (codon 600)
  - Median PFS and OS were estimated by baseline ECOG (PS)

Peeters et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3557)

3557: Survival outcomes in the PRIME study for patients (pts) with *RAS*/*BRAF* wild-type (WT) metastatic colorectal cancer (mCRC), by baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) – Peeters M et al

- **Key results**
  - Longer mPFS/OS in patients receiving panitumumab+FOLFOX4 vs FOLFOX4



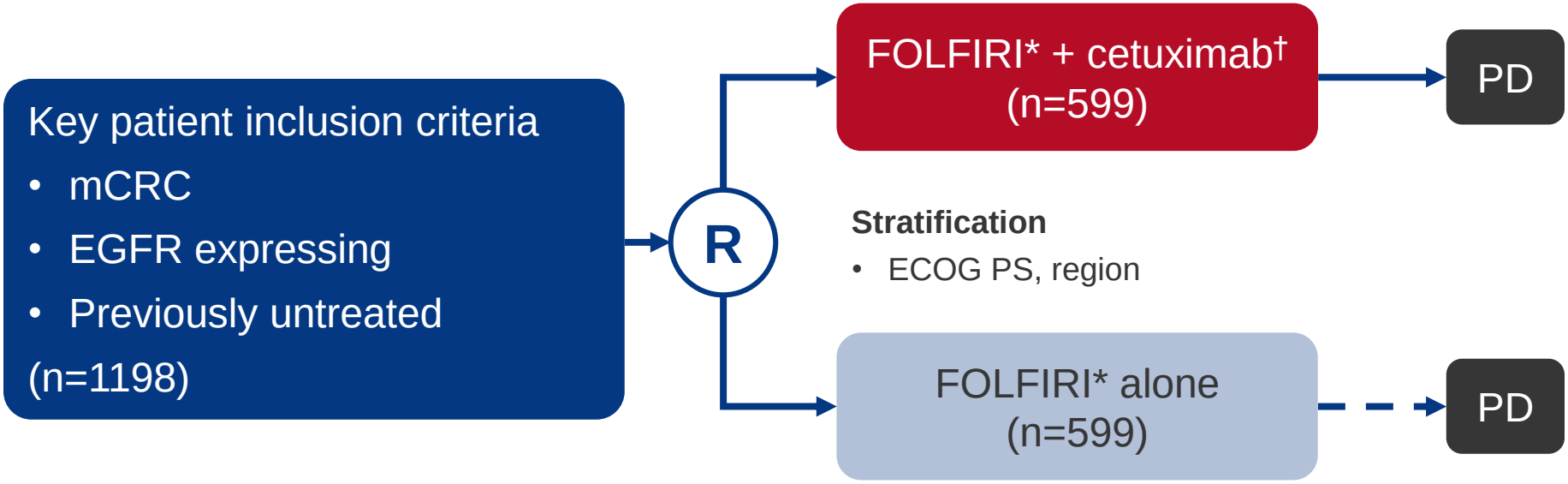


- **Conclusion**
  - **The PFS/OS benefits observed in patients with *RAS*/*BRAF* wild-type mCRC receiving panitumumab+FOLFOX4 are mainly confined to those with a baseline ECOG PS of 0/1**

Peeters et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3557)

3506: Treatment outcome according to tumor *RAS* mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to FOLFIRI with/without cetuximab – Ciardiello F … Van Cutsem E et al

- **Study objective**
  - Retrospective analysis to investigate the treatment effect of FOLFIRI+cetuximab vs FOLFIRI alone in patients with mCRC



Primary endpoint

- PFS

Secondary endpoint

- OS

*Irinotecan 180 mg/m^2 day 1, leucovorin 200 mg/m^2 day 1, 5-FU 400 mg/m^2 bolus then 2400 mg/m^2 infusion over 46 h; †cetuximab 400 mg/m^2 initial dose then 250 mg/m^2 weekly

Ciardiello et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3506)
Presented by Van Cutsem E

3506: Treatment outcome according to tumor *RAS* mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to FOLFIRI with/without cetuximab – Ciardiello F … Van Cutsem E et al

- **Key results**
  - Other *RAS* mutations were detected in 63/430 (15%) patients
  - In those with *RAS* wild-type tumours, a significant benefit across all endpoints was associated with the addition of cetuximab to FOLFIRI (table)

	***RAS* wild-type (all loci)**		**Other *RAS* mutant†**		***RAS* mutant‡ (any locus)**	
Parameter	FOLFOX4+cet **(n=178)**	FOLFOX4 **(n=189)**	FOLFOX4+cet **(n=32)**	FOLFOX4 **(n=31)**	FOLFOX4+cet **(n=246)**	FOLFOX4 **(n=214)**
Response rate, %	66.3	38.6	34.4	35.5	31.7	36.0
Odds ratio	3.11		1.02		0.85	
95% CI	2.03, 4.78		0.33, 3.15		0.58, 1.25	
p-value	<0.0001		0.97		0.40	
Median PFS, months	11.4	8.4	7.2	6.9	7.4	7.5
Odds ratio	0.56		0.81		1.10	
95% CI	0.41, 0.76		0.39, 1.67		0.85, 1.42	
p-value	0.0002		0.56		0.47	
Median OS, months	28.4	20.2	18.2	20.7	16.4	17.7
Odds ratio	0.69		1.22		1.05	
95% CI	0.54, 0.88		0.69, 2.16		0.86, 1.28	
p-value	0.0024		0.50		0.64	

†*KRAS* codon 12/13 or other *RAS*; ‡KRAS codon 12/13 wild-type

Ciardiello et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3506)
Presented by Van Cutsem E

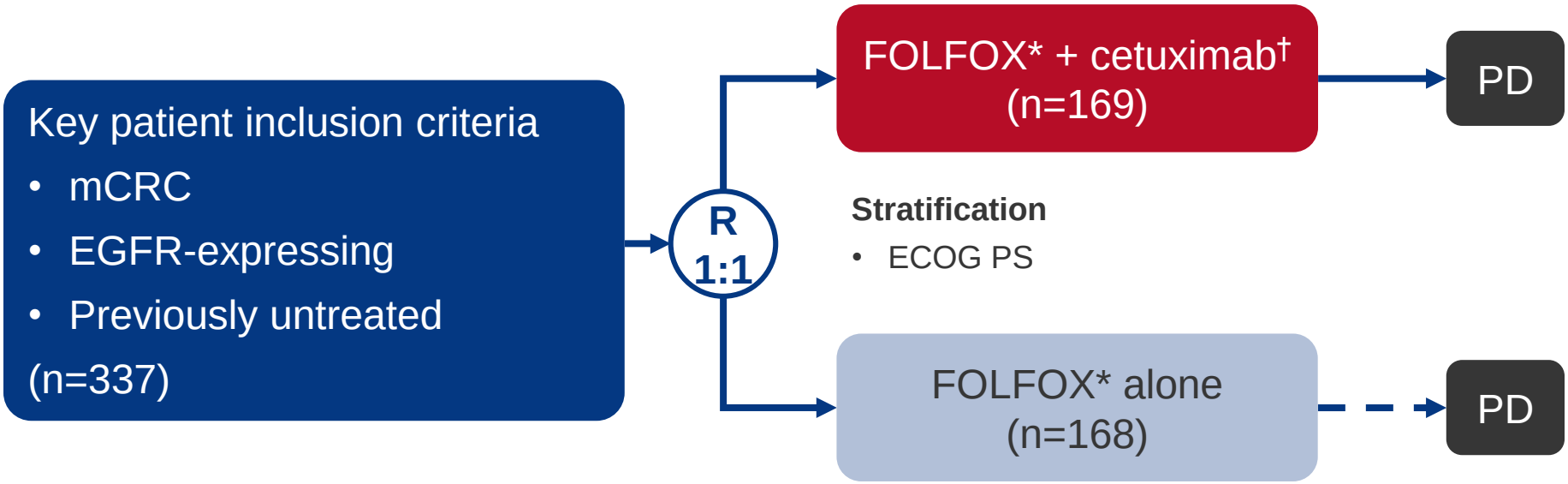
3506: Treatment outcome according to tumor *RAS* mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to FOLFIRI with/without cetuximab – Ciardiello F … Van Cutsem E et al

- **Conclusions**
  - **This study supports the use of FOLFIRI+cetuximab as first-line treatment in patients with *RAS* wild-type mCRC**
    - **Significant improvements in PFS, OS and objective response rate**
    - **No beneficial or deleterious effects were observed with FOLFIRI+cetuximab in patients with *RAS* mutations**
  - **The safety profile in the *RAS* wild-type and *RAS* mutant subgroups was similar and in-line with expectations**
  - **The exclusion of patients with other *RAS* mutations from the *KRAS* codon 12/13 wild-type treatment population improved the benefit-to-risk ratio associated with the addition of cetuximab to FOLFIRI**

Ciardiello et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3506)
Presented by Van Cutsem E

3505: Treatment outcome according to tumor RAS mutation status in OPUS study patients with metastatic colorectal cancer (mCRC) randomized to FOLFOX4 with/without cetuximab – Bokemeyer C et al

- **Study objective**
  - To investigate treatment effect of cetuximab+FOLFOX4 vs FOLFOX4 alone on survival by *KRAS* status (exons 3 and 4) and *NRAS* (exons 2, 3 and 4)



Primary endpoint

- Objective response

Secondary endpoints

- PFS and OS

*Oxaliplatin 85 mg/m^2 day 1, leucovorin 200 mg/m^2 days 1+2, 5-FU 400 mg/m^2 bolus then 600 mg/m^2 infusion days 1+2;
†400 mg/m^2 initial dose then 250 mg/m^2 weekly

Bokemeyer et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3505)

3505: Treatment outcome according to tumor RAS mutation status in OPUS study patients with metastatic colorectal cancer (mCRC) randomized to FOLFOX4 with/without cetuximab – Bokemeyer C et al

- **Key results**
  - In those with *RAS* wild-type tumours, response was significantly improved by the addition of cetuximab to FOLFOX4 (table)

	***RAS* wild-type* (all loci)**		**Other *RAS* mutation†**		***RAS* mutation‡ (any locus)**	
Parameter	FOLFOX4+cet **(n=38)**	FOLFOX4 **(n=49)**	FOLFOX4+cet **(n=15)**	FOLFOX4 **(n=16)**	FOLFOX4+cet **(n=92)**	FOLFOX4 **(n=75)**
Response rate, %	57.9	28.6	53.3	43.8	37.0	50.7
Odds ratio	3.33		1.50		0.58	
95% CI	1.36, 8.17		0.34, 6.53		0.31, 1.08	
p-value	0.0084		0.59		0.0865	
Median PFS, months	12.0	5.8	7.5	7.4	5.6	7.8
Odds ratio	0.53		0.77		1.54	
95% CI	0.27, 1.04		0.28, 2.08		1.04, 2.29	
p-value§	0.0615		0.60		0.0309	
Median OS, months	19.8	17.8	18.4	17.8	13.5	17.8
Odds ratio	0.94		1.09		1.29	
95% CI	0.56, 1.56		0.44, 2.68		0.91, 1.84	
p-value	0.80		0.86		0.1573	

**RAS* evaluable population, n=118; †*KRAS* codon 12/13 or other *RAS*; ‡KRAS codon 12/13 wild-type

Bokemeyer et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3505)

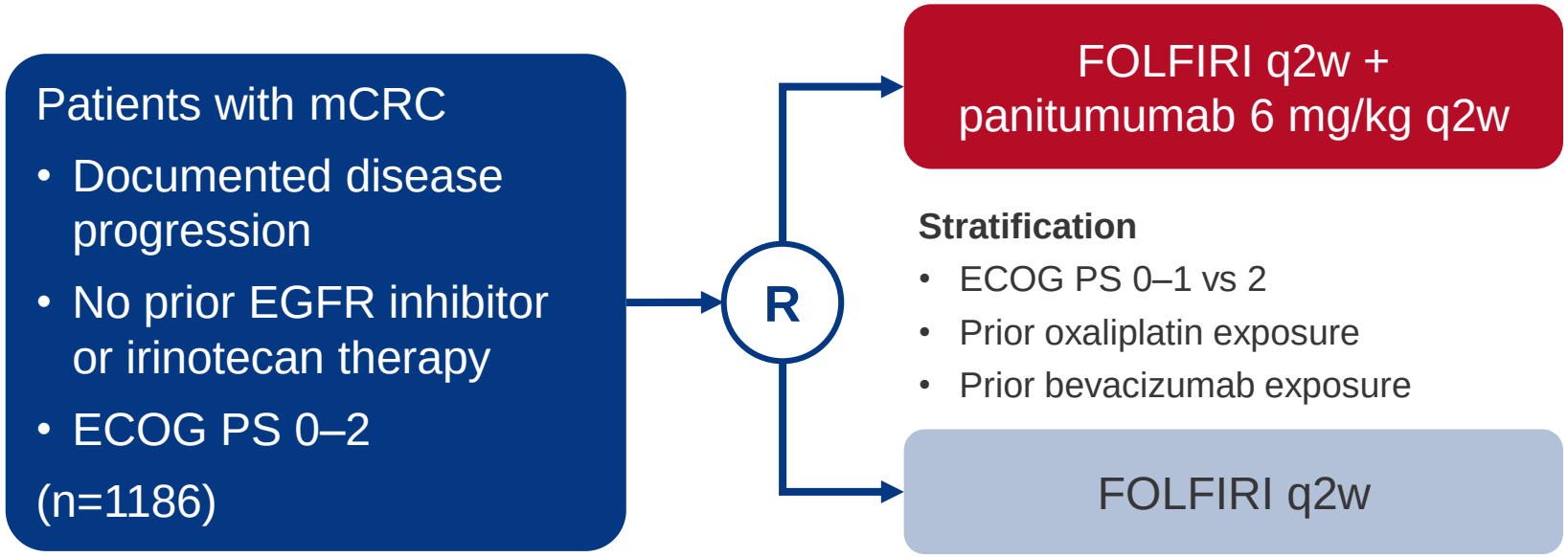
3505: Treatment outcome according to tumor RAS mutation status in OPUS study patients with metastatic colorectal cancer (mCRC) randomized to FOLFOX4 with/without cetuximab – Bokemeyer C et al

- **Conclusions**
  - **In *RAS* wild-type patients, the addition of cetuximab to FOLFOX4 significantly improved objective response rate and has a positive impact on PFS**
  - **In *RAS* mutant patients, combining cetuximab with FOLFOX4 was associated with a negative effect**
  - **The safety profile in the *RAS* wild-type and *RAS* mutant subgroups was similar and in-line with expectations**
  - **Restricting cetuximab administration to patients with *RAS* wild-type tumours might help tailor therapy to maximise patient benefit**

Bokemeyer et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3505)

3568: Updated analysis of *KRAS*/*NRAS* and *BRAF* mutations in study 20050181 of panitumumab (pmab) plus FOLFIRI for second-line treatment (tx) of metastatic colorectal cancer (mCRC) – Peeters M et al

- **Study objective**
  - To retrospectively examine the effects on survival of FOLFIRI+panitumumab compared with FOLFIRI alone in patients with wild-type *KRAS* (exon 2) mCRC based on *RAS/BRAF* mutation status



Primary endpoints

- PFS and OS

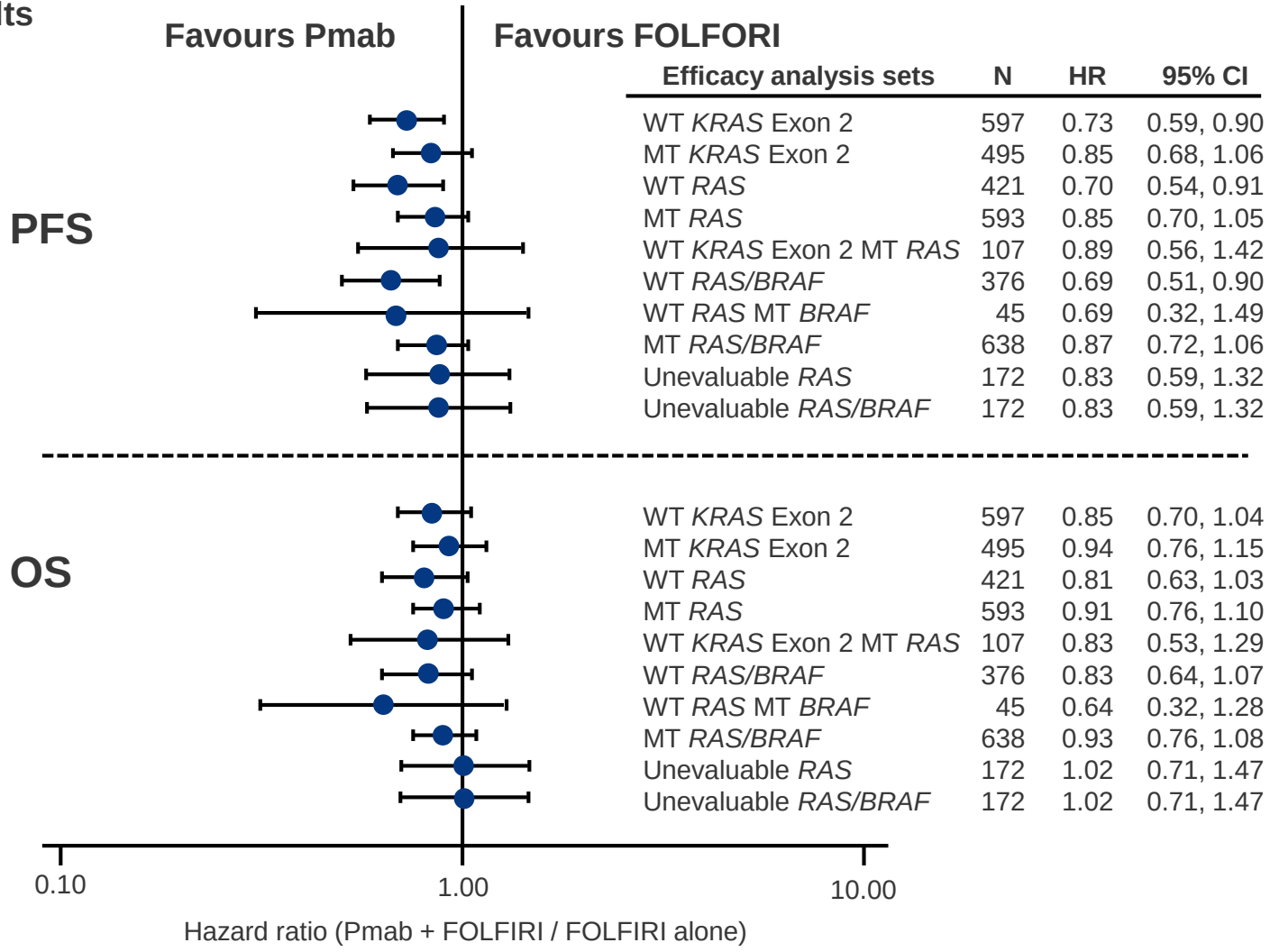
Secondary endpoints

- ORR and safety

Peeters et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3568)

3568: Updated analysis of *KRAS*/*NRAS* and *BRAF* mutations in study 20050181 of panitumumab (pmab) plus FOLFIRI for second-line treatment (tx) of metastatic colorectal cancer (mCRC) – Peeters M et al

- **Key results**



Efficacy analysis sets	N	HR	95% CI
WT *KRAS* Exon 2	597	0.73	0.59, 0.90
MT *KRAS* Exon 2	495	0.85	0.68, 1.06
WT *RAS*	421	0.70	0.54, 0.91
MT *RAS*	593	0.85	0.70, 1.05
WT *KRAS* Exon 2 MT *RAS*	107	0.89	0.56, 1.42
WT *RAS/BRAF*	376	0.69	0.51, 0.90
WT *RAS* MT *BRAF*	45	0.69	0.32, 1.49
MT *RAS/BRAF*	638	0.87	0.72, 1.06
Unevaluable *RAS*	172	0.83	0.59, 1.32
Unevaluable *RAS/BRAF*	172	0.83	0.59, 1.32
WT *KRAS* Exon 2	597	0.85	0.70, 1.04
MT *KRAS* Exon 2	495	0.94	0.76, 1.15
WT *RAS*	421	0.81	0.63, 1.03
MT *RAS*	593	0.91	0.76, 1.10
WT *KRAS* Exon 2 MT *RAS*	107	0.83	0.53, 1.29
WT *RAS/BRAF*	376	0.83	0.64, 1.07
WT *RAS* MT *BRAF*	45	0.64	0.32, 1.28
MT *RAS/BRAF*	638	0.93	0.76, 1.08
Unevaluable *RAS*	172	1.02	0.71, 1.47
Unevaluable *RAS/BRAF*	172	1.02	0.71, 1.47

Peeters et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3568)

3568: Updated analysis of *KRAS*/*NRAS* and *BRAF* mutations in study 20050181 of panitumumab (pmab) plus FOLFIRI for second-line treatment (tx) of metastatic colorectal cancer (mCRC) – Peeters M et al

- **Conclusions**
  - **Improvements in OS and PFS were observed with panitumumab+FOLFIRI vs FOLFIRI alone in wild-type *RAS* group vs wild-type *KRAS* exon 2 group**
  - **Patients with mutant *RAS* mCRC are unlikely to benefit by the addition of panitumumab to FOLFIRI, similar to patients with mutant *KRAS* exon 2 mCRC**
  - ***BRAF* mutations appear to be associated with reduced OS among patients without *RAS* mutations regardless of treatment arm**
  - **These findings support *RAS* testing to determine which patients with mCRC should potentially receive panitumumab treatment**

Peeters et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3568)

3538: Early predictors of prolonged overall survival (OS) in patients (pts) on first-line chemotherapy (CT) for metastatic colorectal cancer (mCRC): An ARCAD study with individual patient data (IPD) on 10,962 pts – Sommeijer DW et al

- **Study objective**
  - To evaluate at the patient level the association between early response-based endpoints vs long-term outcomes in patients with mCRC treated with first-line CT
- **Study design**
  - A retrospective analysis of data from 10,962 patients from 16 phase III trials in the ARCAD database
  - Patients were treated with 5FU-LV/capecitabine±oxaliplatin/irinotecan
  - Early response at 6, 8/9 or 12 weeks, measured as:
    - Early tumour shrinkage (≥20% decrease from baseline)
    - Early objective tumour response (CR/PR by RECIST)
    - Early non-progression status (CR/PR/SD by RECIST)

    were correlated with best overall response and confirmed response within the initial 26 weeks of treatment

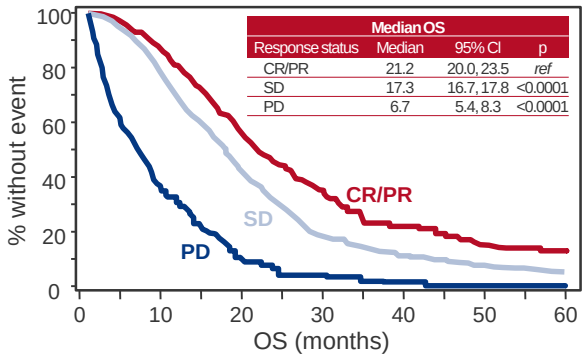
Sommeijer et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3538)

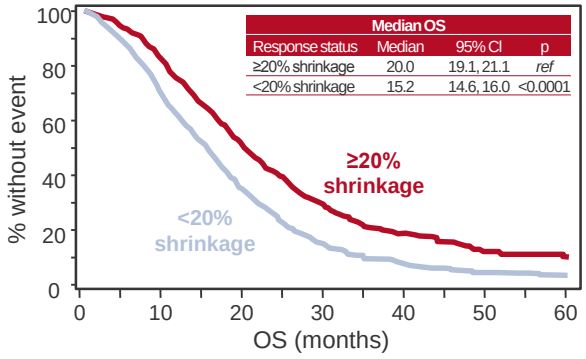
3538: Early predictors of prolonged overall survival (OS) in patients (pts) on first-line chemotherapy (CT) for metastatic colorectal cancer (mCRC): An ARCAD study with individual patient data (IPD) on 10,962 pts – Sommeijer DW et al

- **Key results**

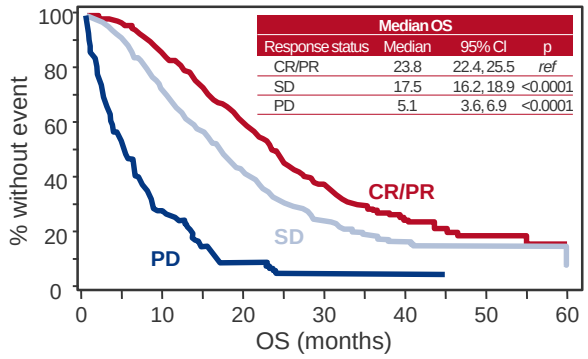
OS by early response status

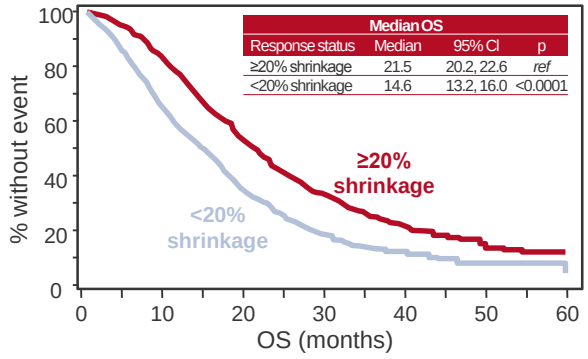
6 weeks



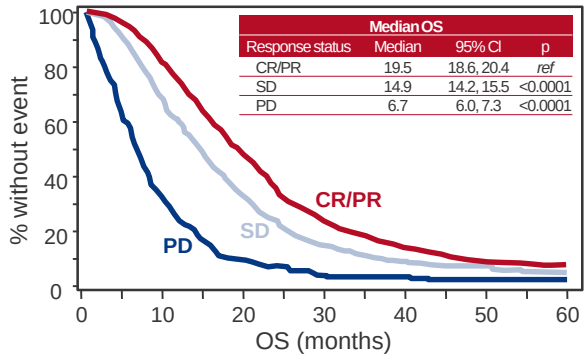


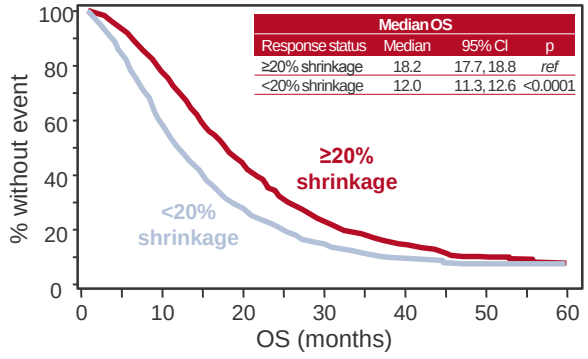
8/9 weeks





12 weeks





- **Conclusions**
  - **Early responses were significantly associated with prolonged OS**
  - **The association between early endpoints and OS was as strong as the associations between standard endpoints and OS**

BOR, best overall response; ConfR, confirmed response

Sommeijer et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3538)

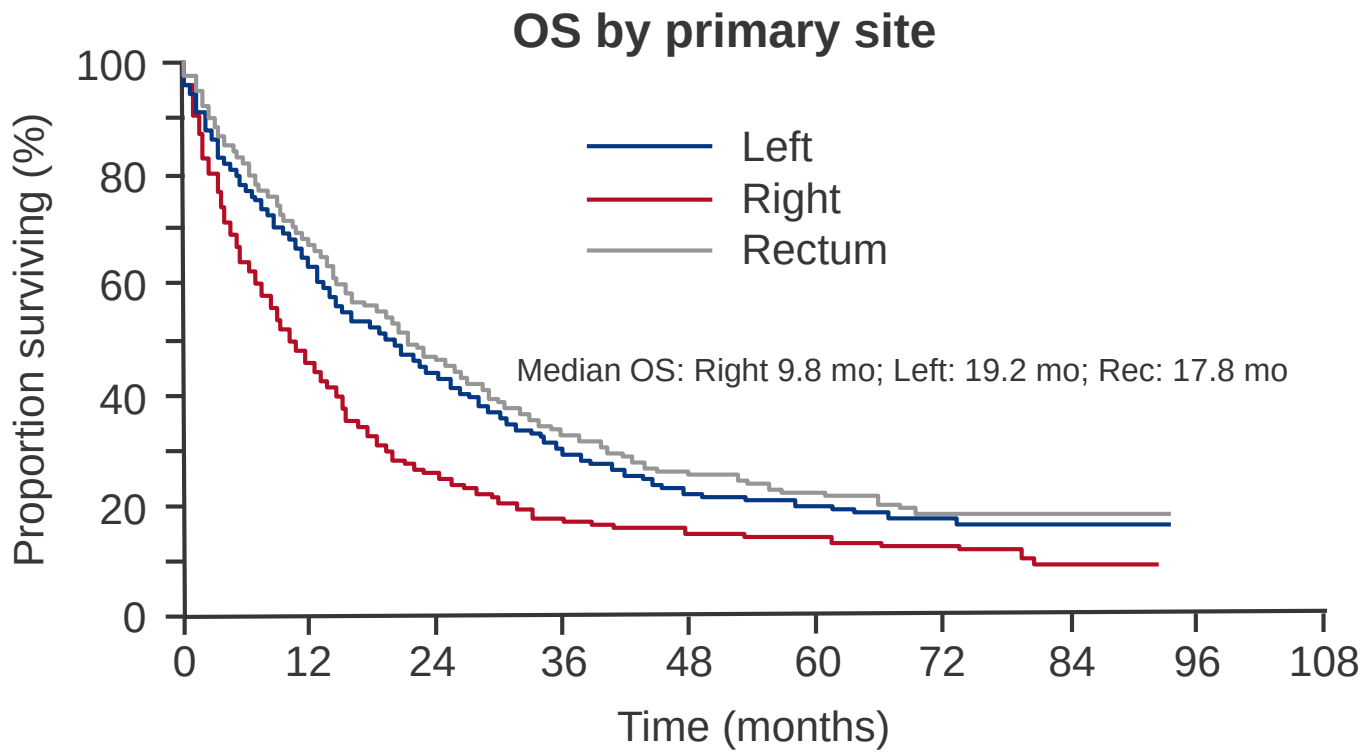
3540: Survival outcomes for patients with metastatic colorectal cancer (mCRC) based on primary site, right (R) colon versus left (L) colon versus rectal (Rec) primary: Results from the South Australian Registry of mCRC – Tomita Y et al

- **Study objective**
  - To explore the association between clinical characteristics of mCRC and the site of the primary tumour
- **Study design**
  - Retrospective study of data from 2972 patients in the South Australian mCRC registry
  - Differences in patient characteristics, treatment received and outcomes were correlated with location of the primary tumour
    - Right colon (n=1046; caecum to transverse colon)
    - Left colon (n=1103; splenic flexure to sigmoid)
    - Rectal (n=823)
- Kaplan-Meier was used for survival outcomes and Cox proportional hazards regression modeling was used to assess defined prognostic markers

Tomita et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3540)

3540: Survival outcomes for patients with metastatic colorectal cancer (mCRC) based on primary site, right (R) colon versus left (L) colon versus rectal (Rec) primary: Results from the South Australian Registry of mCRC – Tomita Y et al

- **Key results**

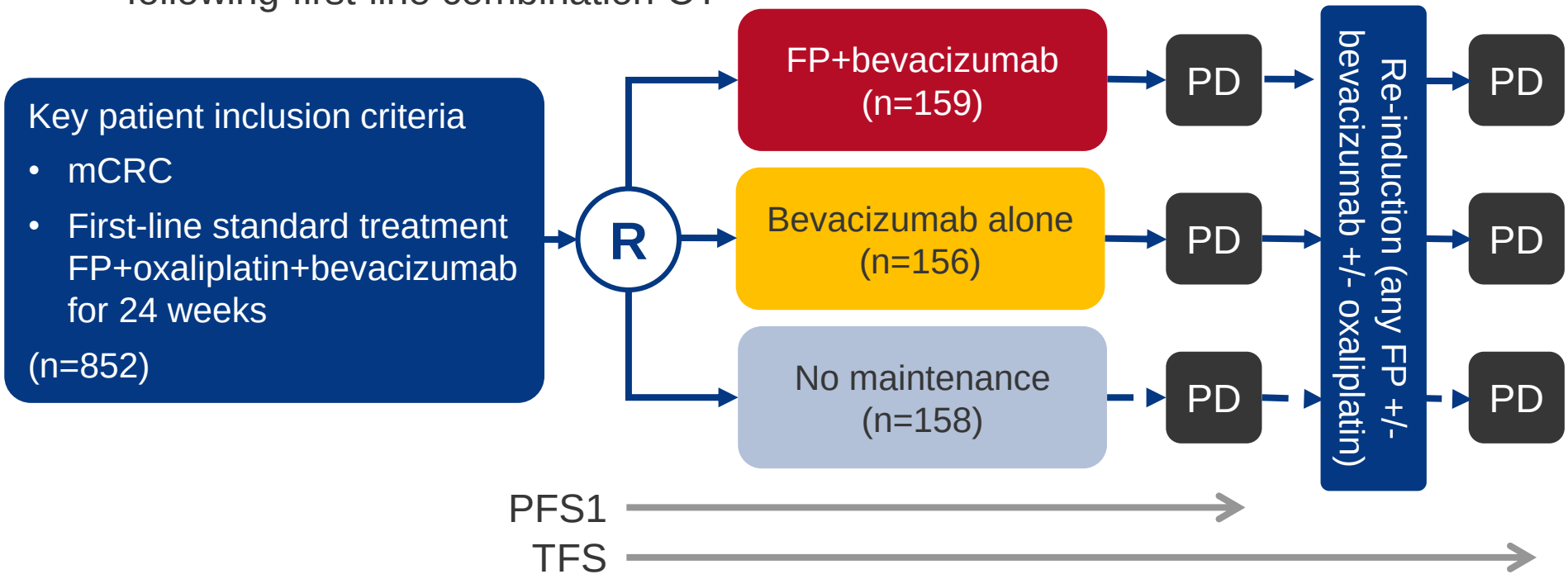


- **Conclusion**
  - **Right colon primary mCRC was associated with less favourable prognostic factors and poorer outcomes than left colon/rectal primary mCRC**

Tomita et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3540)

3503: Maintenance strategy with fluoropyrimidines (FP) plus Bevacizumab (Bev), Bev alone, or no treatment, following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastatic colorectal cancer (mCRC): A phase III non-inferiority trial (AIO KRK 0207) – Arnold D et al

- **Study objective**
  - To investigate the optimal maintenance strategy in patients with mCRC following first-line combination CT



Primary endpoint
- TFS

Secondary endpoints
- PFS1, OS and toxicity

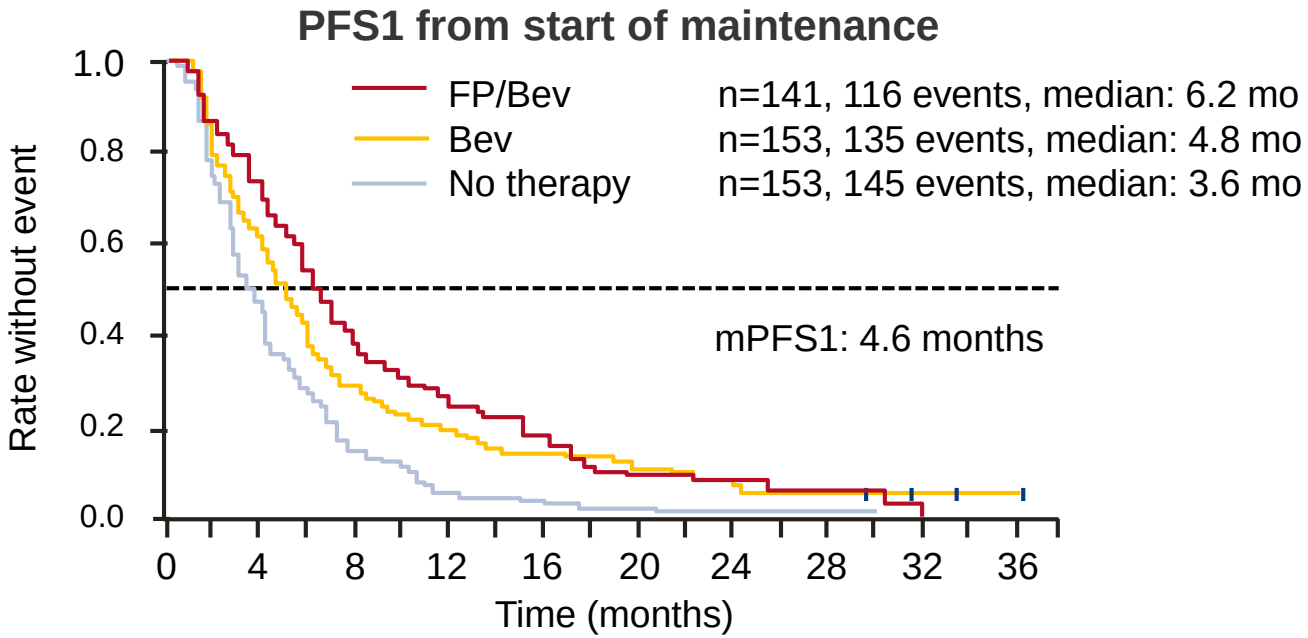
Stratification
- Adjuvant treatment, CR/PR vs SD, ECOG PS

FP, fluoropyrimidines; PFS1, time to first progression; TFS, time to failure of strategy

Arnold et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3503)

3503: Maintenance strategy with fluoropyrimidines (FP) plus Bevacizumab (Bev), Bev alone, or no treatment, following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastatic colorectal cancer (mCRC): A phase III non-inferiority trial (AIO KRK 0207) – Arnold D et al

- **Key results**
  - PFS1 improved with treatment intensity and FP/bevacizumab was better than bevacizumab alone and this was better than no treatment



B vs A: HR (95% CI) 1.21 (0.95, 1.56); log rank p=0.13
C vs A: HR (95% CI) 2.06 (1.60, 2.66); log rank p<0.001
C vs B: HR (95% CI) 1.57 (1.24, 1.99); log rank p<0.001
Log rank test: p<0.0001

Arnold et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3503)

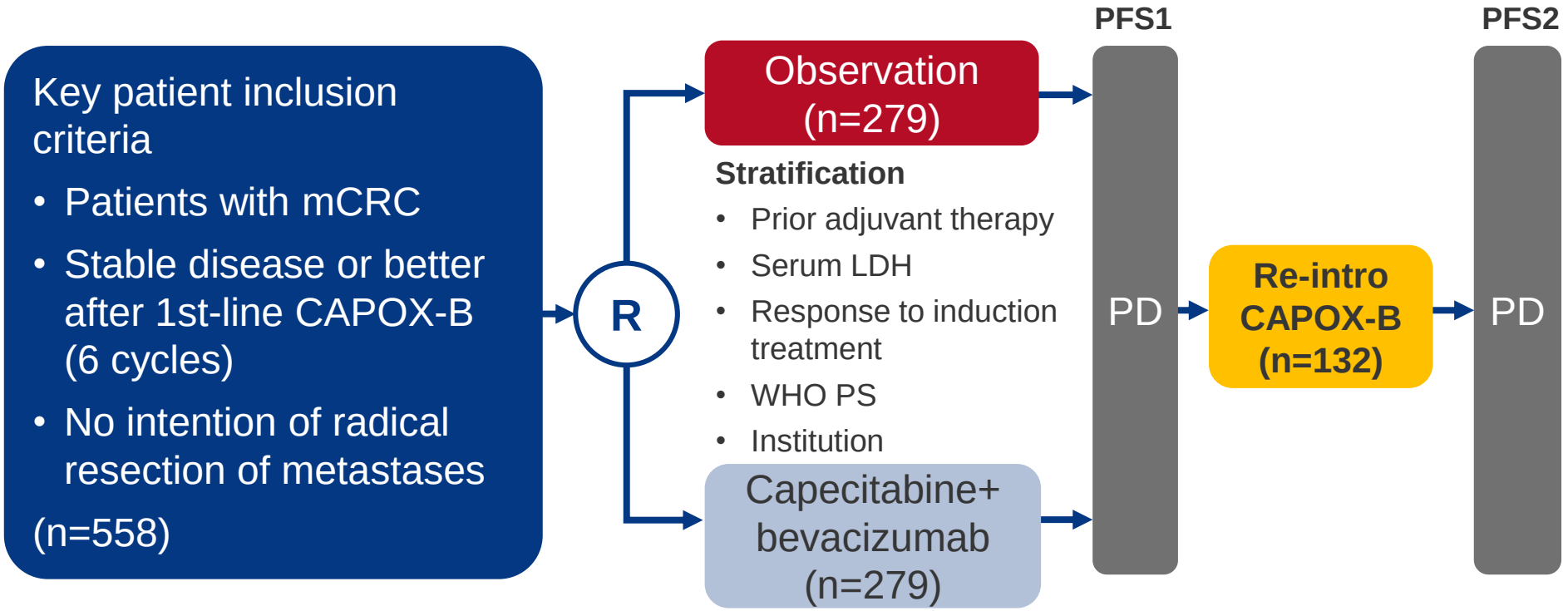
3503: Maintenance strategy with fluoropyrimidines (FP) plus Bevacizumab (Bev), Bev alone, or no treatment, following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastatic colorectal cancer (mCRC): A phase III non-inferiority trial (AIO KRK 0207) – Arnold D et al

- **Conclusions**
  - **Using a TFS strategy following 6 months of induction with CT demonstrated that**
    - **Maintenance with bevacizumab is non-inferior to FP/bevacizumab**
    - **Non-inferiority cannot be concluded for no active treatment**
  - **FP plus bevacizumab or bevacizumab alone, showed prolonged TFS over no treatment**
  - **Only a minority of patients received re-induction treatment as planned**
  - **Preliminary OS showed no difference between the treatment arms**

Arnold et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3503)

3504: Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine + bevacizumab versus observation after induction treatment with chemotherapy + bevacizumab in metastatic colorectal cancer (mCRC) – Koopman M et al

- **Study objective**
  - To examine the efficacy of observation vs maintenance treatment with capecitabine+bevacizumab after induction treatment with CAPOX-B; 6 cycles



Primary endpoint

- PFS2

CAPOX-B, capecitabine, oxaliplatin+bevacizumab

Koopman et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3504)

3504: Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine + bevacizumab versus observation after induction treatment with chemotherapy + bevacizumab in metastatic colorectal cancer (mCRC) – Koopman M et al

- **Key results**

	Observation (95% CI), mo	Maintenance (95% CI), mo	HR (95% CI)	p-value
Median PFS1	4.1 (3.9, 4.2)	8.5 (6.5, 10.3)	0.43 (0.36, 0.52)	<0.0001
Median PFS2	8.5 (7.4, 10.4)	11.7 (10.1, 13.3)	0.67 (0.56, 0.81)	<0.0001
TT2PD	11.1 (10.3, 12.6)	13.9 (12.3, 15.6)	0.68 (0.57, 0.82)	<0.0001
Median OS	18.1 (16.3, 20.2)	21.6 (19.4, 23.8)	0.89 (0.73, 1.07)	0.22

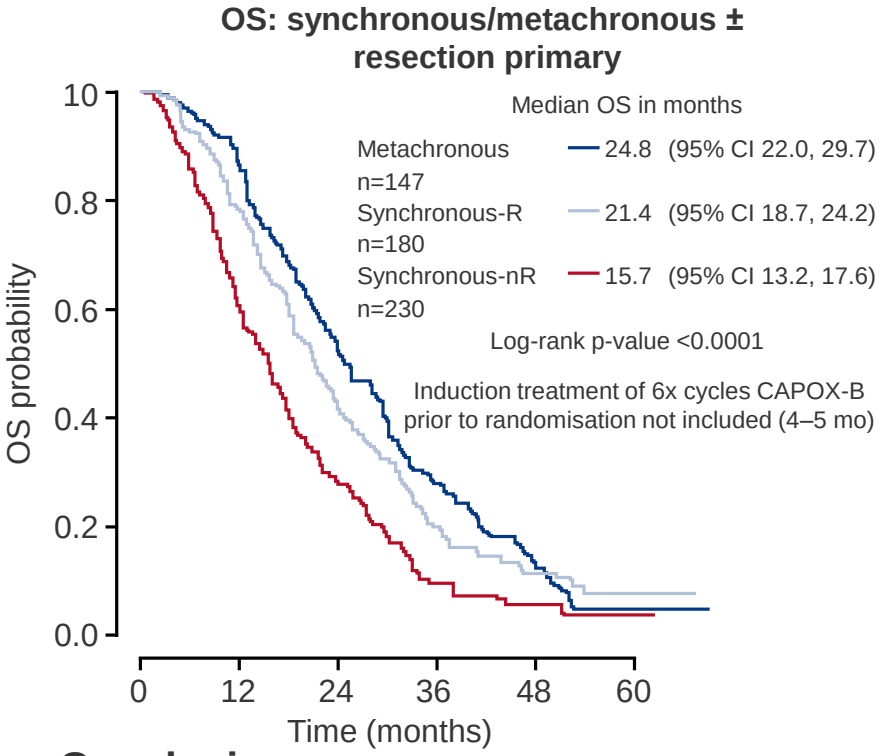
  - QoL was maintained during maintenance treatment and was clinically not inferior vs the observation arm (between group difference 3.9 [95% CI 1.2, 6.5]; p=0.004)
  - A subgroup analysis showed significant survival effects for the following factors:
    - [PFS2]: Treatment arm, response to induction therapy, serum LDH and metachronous vs synchronous with/without resection of primary tumour
    - [OS]: Treatment arm, response to induction therapy, WHO PS, site of primary tumour and metachronous vs synchronous with/without resection of primary tumour

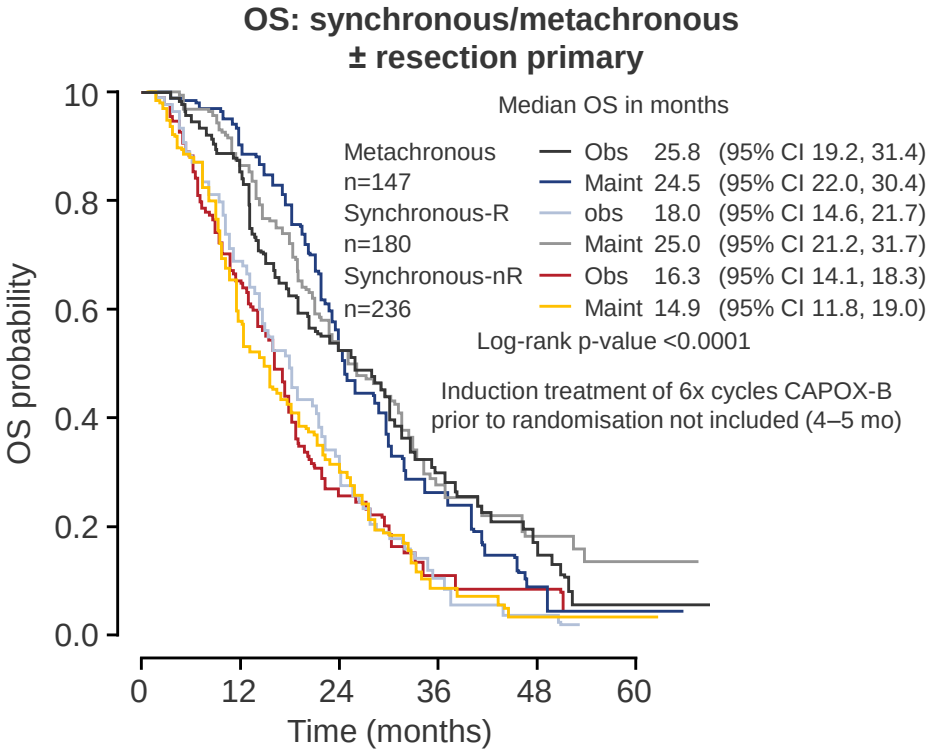
TT2PD, time to second progression of disease, time from randomisation to progression upon any treatment given after PFS1

Koopman et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3504)

3504: Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine + bevacizumab versus observation after induction treatment with chemotherapy + bevacizumab in metastatic colorectal cancer (mCRC) – Koopman M et al

- **Key results**





- **Conclusions**
  - **Benefits were observed in all subgroups for PFS2, PFS1 and TT2PD**
  - **Patients with synchronous disease with resected primary tumour and patients with a CR/PR as best response to induction treatment may benefit most from maintenance treatment in terms of OS**

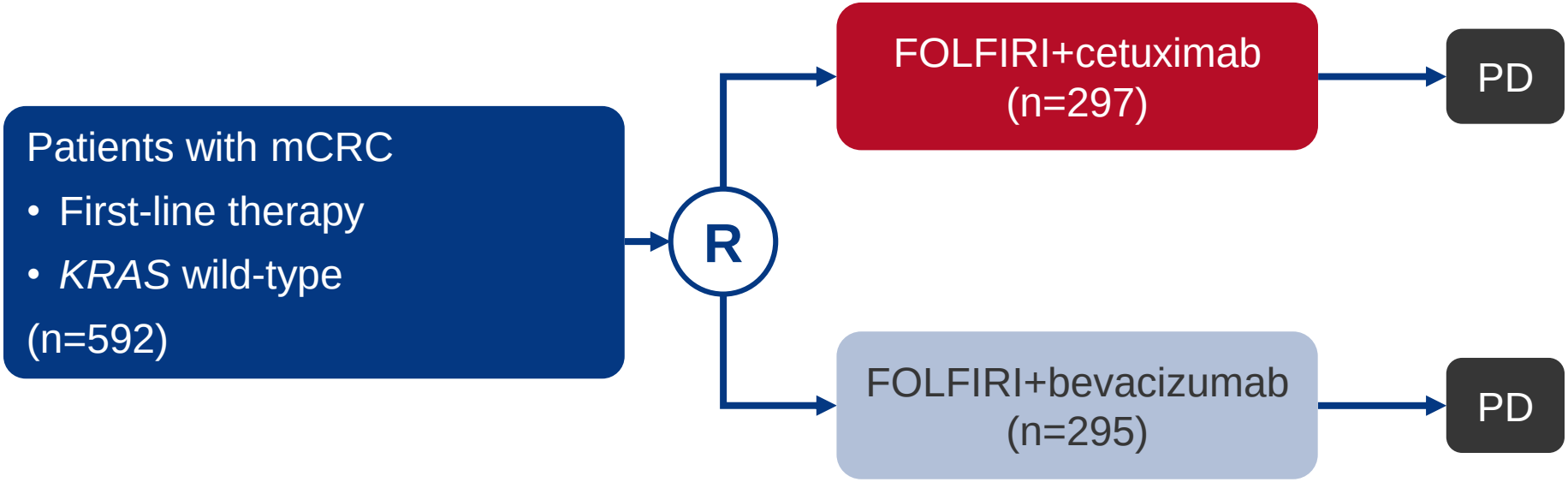
Koopman et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3504)

COLORECTAL CANCER

BIOMARKERS

445: Mutations within the EGFR signaling pathway: Influence on efficacy in FIRE-3—A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) – Stintzing S et al

- **Study objective**
  - To investigate the influence of mutations on the efficacy of cetuximab in addition to standard CT in patients with mCRC



Primary endpoint

- ORR

FOLFIRI q2w, 5-FU: 400 mg/m^2 (IV bolus), folinic acid 400 mg/m^2, irinotecan 180 mg/m^2; 5-FU 2400 mg/m^2 (IV 46 h)
Cetuximab: 400 mg/m^2 IV 120 min initial dose, then 250 mg/^{2} IV 60 min q1w
Bevacizumab: 5 mg/kg IV 30–90 I q2w

Stintzing et al. J Clin Oncol 2014; 32 (suppl 3; abstr 445)

445: Mutations within the EGFR signaling pathway: Influence on efficacy in FIRE-3—A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) – Stintzing S et al

- **Key results**
  - Frequency of mutations in the EGFR pathway

Exon	1	2	3	4	9	11	15	20	E17K
KRAS, %		wt	4.3	4.9					
NRAS, %		3.8	2	0					
BRAF, %						0	10		
PIK3CA, %					5.3			2.0	
AKT, %									0.9

Stintzing et al. J Clin Oncol 2014; 32 (suppl 3; abstr 445)

445: Mutations within the EGFR signaling pathway: Influence on efficacy in FIRE-3—A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) – Stintzing S et al

- **Key results**

ORR	FOLFIRI+ cetuximab % (95% CI)	FOLFIRI+ bevacizumab % (95% CI)	Odds ratio (95% CI)	p-value
KRAS exon 2 WT (ITT; n=592)	62.0 (56.2, 67.5)	58.0 (52.1, 63.7)	1.18 (0.85, 1.64)	0.183
RAS WT (n=342)	65.5 (57.9, 72.6)	59.6 (51.9, 67.1)	1.28 (0.83, 1.99)	0.32
RAS MT (n=65)	38.2 (22.2, 56.4)	58.1 (39.1, 75.5)	0.45 (0.17, 1.21)	0.14
KRAS exon 2 MT & RAS MT (n=178)	38.0 (28.1, 48.8)	52.1 (40.1, 62.1)	0.59 (0.32, 1.06)	0.097
BRAF mutant (n=48)	52.2 (30.6, 73.2)	40.0 (21.1, 61.3)	1.64 (0.52, 5.14)	0.29
PIK3CA mutant (n=38)	47.4 (24.4, 71.1)	57.0 (33.5, 79.7)	0.65 (0.18, 2.36)	0.84

Stintzing et al. J Clin Oncol 2014; 32 (suppl 3; abstr 445)

445: Mutations within the EGFR signaling pathway: Influence on efficacy in FIRE-3—A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) – Stintzing S et al

- **Key results**

PFS		FOLFIRI+ cetuximab	FOLFIRI+ bevacizumab	HR (95% CI)	p-value
KRAS exon 2 WT (ITT; n=592)	Events, n/N (%) Median (95% CI), mo	250/297 (84.2) 10.0 (8.8, 10.8)	242/295 (82.0) 10.3 (9.8, 11.3)	1.06 (0.88, 1.26)	0.547
RAS WT (n=342)	Events, n/N (%) Median (95% CI), mo	144/171 (84.2) 10.4 (9.5, 12.2)	143/171 (83.6) 10.2 (9.3, 11.5)	0.93 (0.74, 1.17)	0.54
BRAF mutant (n=48)	Events, n/N (%) Median (95% CI), mo	22/23 (95.7) 4.9 (2.4, 8.8)	25/25 (100) 6.0 (4.3, 7.8)	0.87 (0.49, 1.57)	0.65
PIK3CA mutant (n=38)	Events, n/N (%) Median (95% CI), mo	18/19 (94.7) 7.8 (5.1, 10.8)	15/19 (78.9) 13.3 (4.9, 28.9)	1.61 (0.80, 3.25)	0.18
OS					
KRAS exon 2 WT (ITT; 592)	Events, n/N (%) Median (95% CI), mo	158/297 (53.2) 28.7 (24.0, 36.6)	185/295 (62.7) 25.0 (22.7, 27.6)	0.77 (0.62, 0.96)	0.017
RAS WT (n=342)	Events, n/N (%) Median (95% CI), mo	91/171 (53.2) 33.1 (24.5, 39.4)	110/171 (64.3) 25.6 (22.7, 28.6)	0.70 (0.53, 0.92)	0.011
BRAF mutant (n=48)	Events, n/N (%) Median (95% CI), mo	18/23 (78.3) 12.3 (5.5, 21.7)	24/25 (96.0) 13.7 (7.8, 19.5)	0.87 (0.47, 1.61)	0.65
PIK3CA mutant (n=38)	Events, n/N (%) Median (95% CI), mo	13/19 (68.4) 26.5 (14.2, 30.6)	11/19 (57.9) 25.9 (21.0, 33.2)	1.08 (0.48, 2.43)	0.86

Stintzing et al. J Clin Oncol 2014; 32 (suppl 3; abstr 445)

445: Mutations within the EGFR signaling pathway: Influence on efficacy in FIRE-3—A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) – Stintzing S et al

- **Conclusions**
  - **Comparable findings for ORR and PFS were found in both treatment groups in patients with all-RAS wild-type tumours**
  - **Patients with all-RAS wild-type tumours who received cetuximab as first-line therapy had a markedly superior OS**
  - **In patients with RAS-mutant tumours there was no difference between treatment with FOLFIRI+cetuximab or FOLFIRI+bevacizumab**
  - **Comparable findings for ORR, PFS and OS were demonstrated in patients with BRAF mutant tumours between the two treatment groups**
  - **For patients with PIK3CA mutant tumours comparable findings were observed for ORR and OS between the two treatment groups**
  - **In patients with PIK3CA mutant tumours PFS was longer (but not significantly) in those who received FOLFIRI+bevacizumab compared with FOLFIRI+cetuximab**
  - **It is recommended that RAS (KRAS and NRAS) mutation status should be determined upfront in patients with mCRC**

Stintzing et al. J Clin Oncol 2014; 32 (suppl 3; abstr 445)

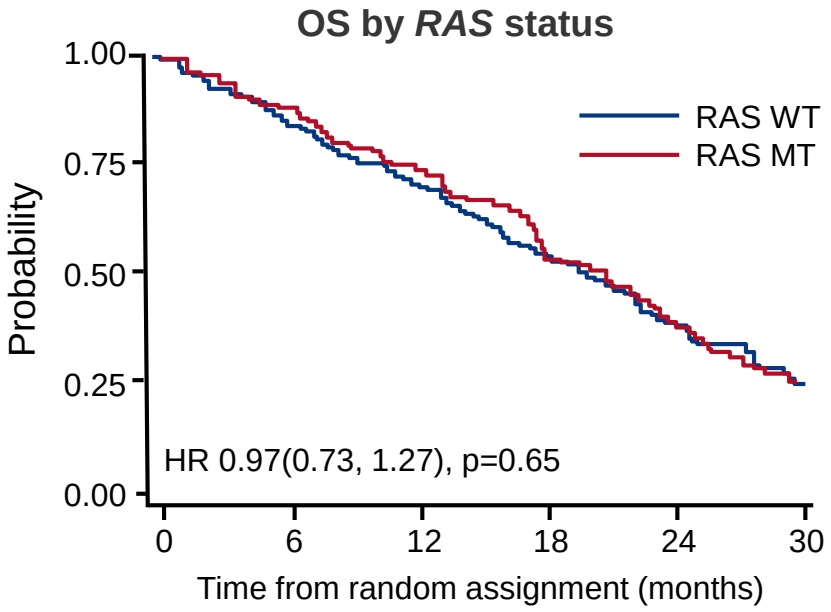
3539: Correlation of *PI3KCA* and extended *RAS* gene mutation status with outcomes from the phase III AGITG MAX involving capecitabine (C) along or in combination with bevacizumab (B) with or without mitomycin C (M) advanced colorectal cancer (CRC) – Price TJ et al

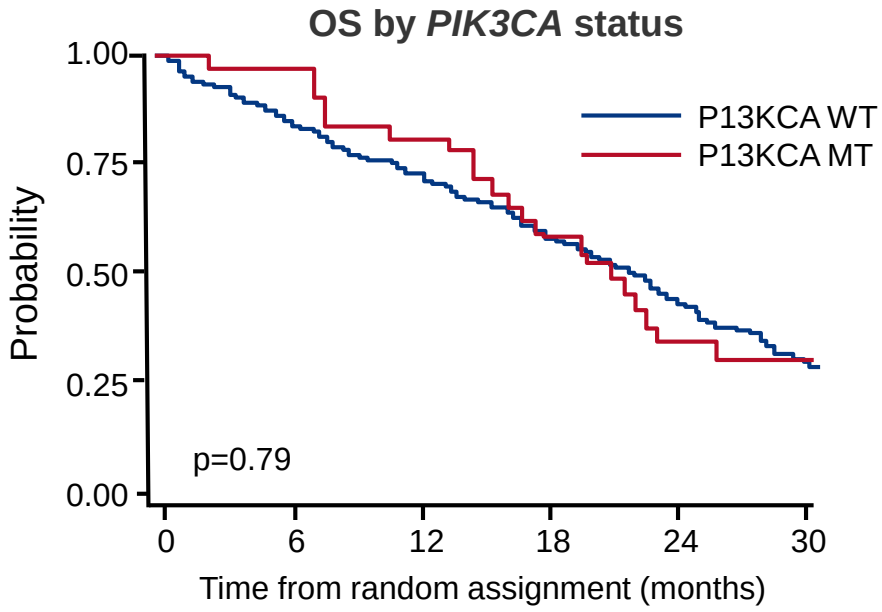
- **Study objective**
  - To investigate the prognostic and predictive value of extended *RAS* and *PI3KCA* mutation status in patients with advanced CRC treated with capecitabine± bevacizumab±mitomycin C
- **Study design**
  - Randomised phase III study (MAX) of patients with advanced CRC who were randomly allocated to capecitabine alone or in combination with bevacizumab with or without mitomycin C
  - DNA macrodissected from archival formalin-fixed paraffin-embedded tumour tissue
  - Mutation status for *KRAS* and *NRAS* (both exons 2, 3, 4) determined using pyrosequencing and confirmed with Sanger sequencing (for equivocal *RAS*)
  - Mutation status (wild-type vs mutated) was correlated with efficacy outcomes (RR, PFS and OS)
  - Predictive analyses were undertaken using a test for interaction

Price et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3539)

3539: Correlation of *PI3KCA* and extended *RAS* gene mutation status with outcomes from the phase III AGITG MAX involving capecitabine (C) along or in combination with bevacizumab (B) with or without mitomycin C (M) advanced colorectal cancer (CRC) – Price TJ et al

- **Key results**
  - The total proportion with any *RAS* mutant was 40.9%
  - *PI3K* mutant rate was 7.5% for exon 9, and 3.6% for exon 20
  - *RAS* status (wild-type vs mutated) had no prognostic impact for PFS (HR 0.92)
  - *RAS* status did not predict efficacy of bevacizumab for PFS (p=0.51)
  - *PI3KCA* mutation was neither predictive for bevacizumab effect nor prognostic





Price et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3539)

3539: Correlation of *PI3KCA* and extended *RAS* gene mutation status with outcomes from the phase III AGITG MAX involving capecitabine (C) along or in combination with bevacizumab (B) with or without mitomycin C (M) advanced colorectal cancer (CRC) – Price TJ et al

- **Conclusions**
  - ***RAS* or *PI3KCA* mutation status did not appear to have any therapeutic implication when bevacizumab was given in addition to capecitabine CT**
  - ***RAS* or *PI3KCA* mutation status was not prognostic for PFS or OS, or predictive of bevacizumab outcome in patients with advanced CRC**
  - **A clinically relevant proportion of patients (11.2%) considered *KRAS* wild-type have an additional mutation in the *RAS* pathway**

Price et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3539)

3559: Cell-free DNA levels in colorectal cancer patients treated with irinotecan, healthy controls, and non-cancer patients with comorbidity – Spindler K-LG et al

- **Study objective**
  - To investigate the clinical value of total cell free DNA (cfDNA) measurement in patients with mCRC treated with second-line irinotecan monotherapy
- **Study design**
  - Patients with mCRC (n=100) treated with second-line irinotecan were compared with a cohort of healthy controls with and without comorbidity (n=70 and n=100, respectively)
  - Plasma samples drawn prior to the first cycle of chemotherapy and at time of progression were analysed for cfDNA using qPCR

Spindler et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3559)

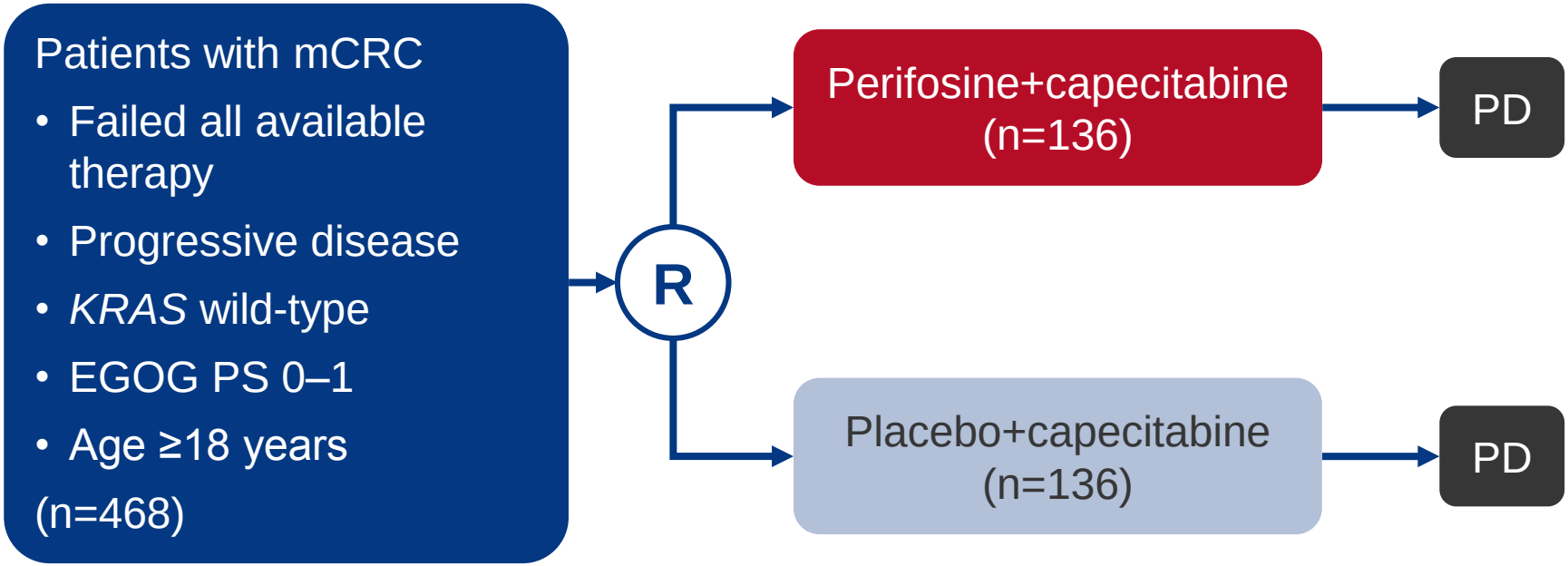
3559: Cell-free DNA levels in colorectal cancer patients treated with irinotecan, healthy controls, and non-cancer patients with comorbidity – Spindler K-LG et al

- **Key results**
  - cfDNA levels were significantly higher in cancer patients compared with control cohort, with a clear capability for discriminating between the groups (AUC 0.82, p<0.0001)
  - Patients with high levels of cfDNA had a shorter outcome compared with those with lower levels according to upper normal limit levels
    - PFS: 2.1 vs 6.5 months for high vs low levels (HR 2.53 [95% CI 1.57, 4.06], p≤0.0001)
    - OS: 7.4 vs 13.8 months for high vs low levels (HR 2.52 [95% CI 1.54, 4.13], p<0.0001)
  - Cox regression multivariate analysis showed a PFS HR of 1.4 (95% CI 1.1, 1.7; p=0.03) for each increase in cfDNA quartile and HR of 1.6 (95% CI 1.3, 2.0; p<0.0001) for OS
- **Conclusion**
  - **Measurement of cfDNA contains important clinical information and may become a useful tool for predicting outcomes from chemotherapy in mCRC**

Spindler et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3559)

3606: Impact of PI3K aberrations on efficacy of perifosine (P), x-PECT: A phase III randomized study of P plus capecitabine (PC) versus placebo plus capecitabine (C) in refractory metastatic colorectal cancer (mCRC) patients – Eng C et al

- **Study objective**
  - To investigate whether patients with *PI3K* aberrations (*PIK3CA* and PTEN loss) would show better outcomes with perifosine, a synthetic alkylphospholipid that affects signalling pathways including PI3K/Akt, PTEN and NF-κB



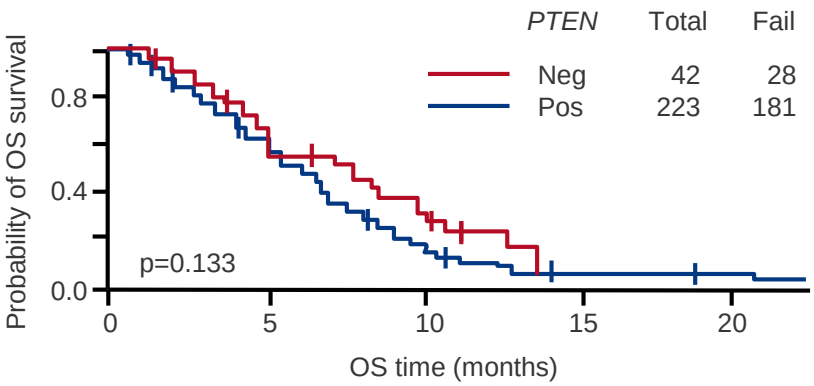
Primary endpoint

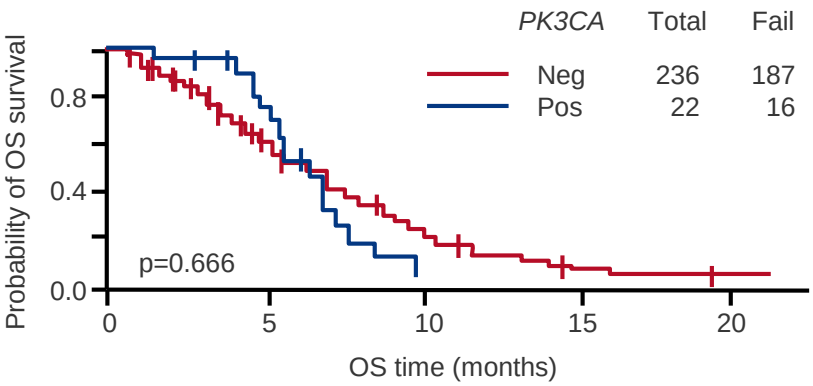
- OS

Eng et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3606)

3606: Impact of PI3K aberrations on efficacy of perifosine (P), x-PECT: A phase III randomized study of P plus capecitabine (PC) versus placebo plus capecitabine (C) in refractory metastatic colorectal cancer (mCRC) patients – Eng C et al

- **Key results**
  - 45% of all patients had a *KRAS* mutation; *NRAS* (1%); *BRAF* (3%); *PIK3CA* (9%); *Akt* (<1%) and loss of PTEN (16%) by IHC
  - *PIK3CA* mutation or loss of PTEN occurred in 25% of patients





- **Conclusions**
  - **There was no improvement in OS with perifosine+capecitabine vs capecitabine alone**
  - **The presence of a *PI3K* aberration (*PIK3CA* and PTEN loss) did not appear to be associated with an improved efficacy of perifosine**

Eng et al. J Clin Oncol 2014; 32 (suppl 5; abstr 3606)

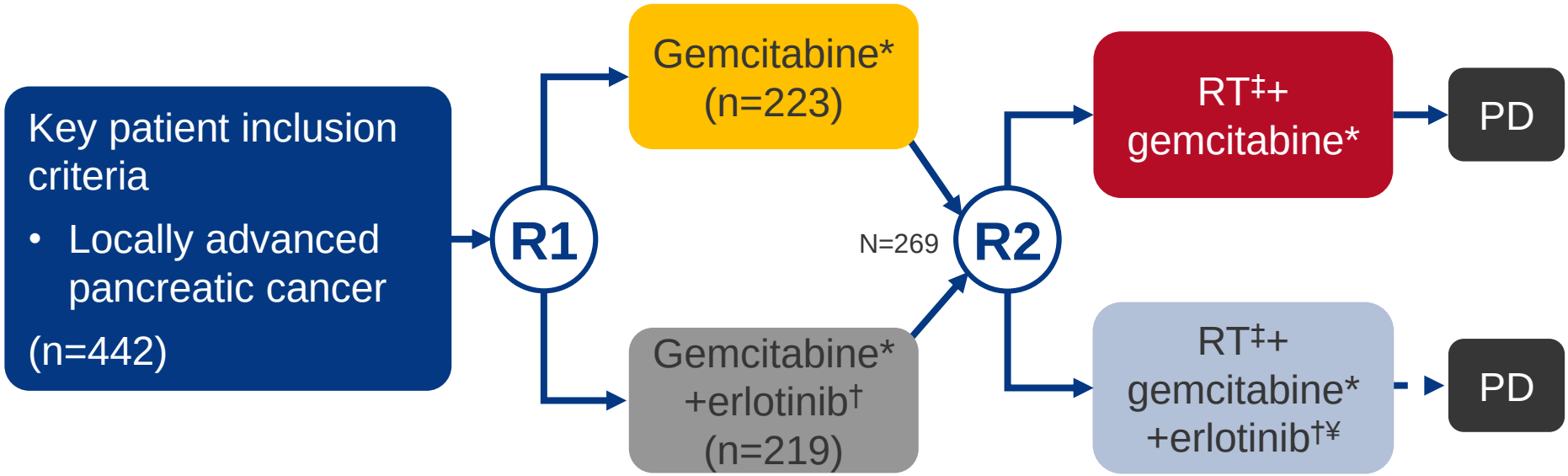
PANCREATIC CANCER & HEPATOBILIARY TUMOURS

PANCREATIC CANCER

NEOADJUVANT THERAPY

4001: Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study – Huguet F et al

- **Study objective**
  - To determine whether OS is improved with CRT in patients with locally advanced pancreatic cancer whose tumour is controlled after 4 months of induction CT



Primary endpoint

- OS

Secondary endpoints

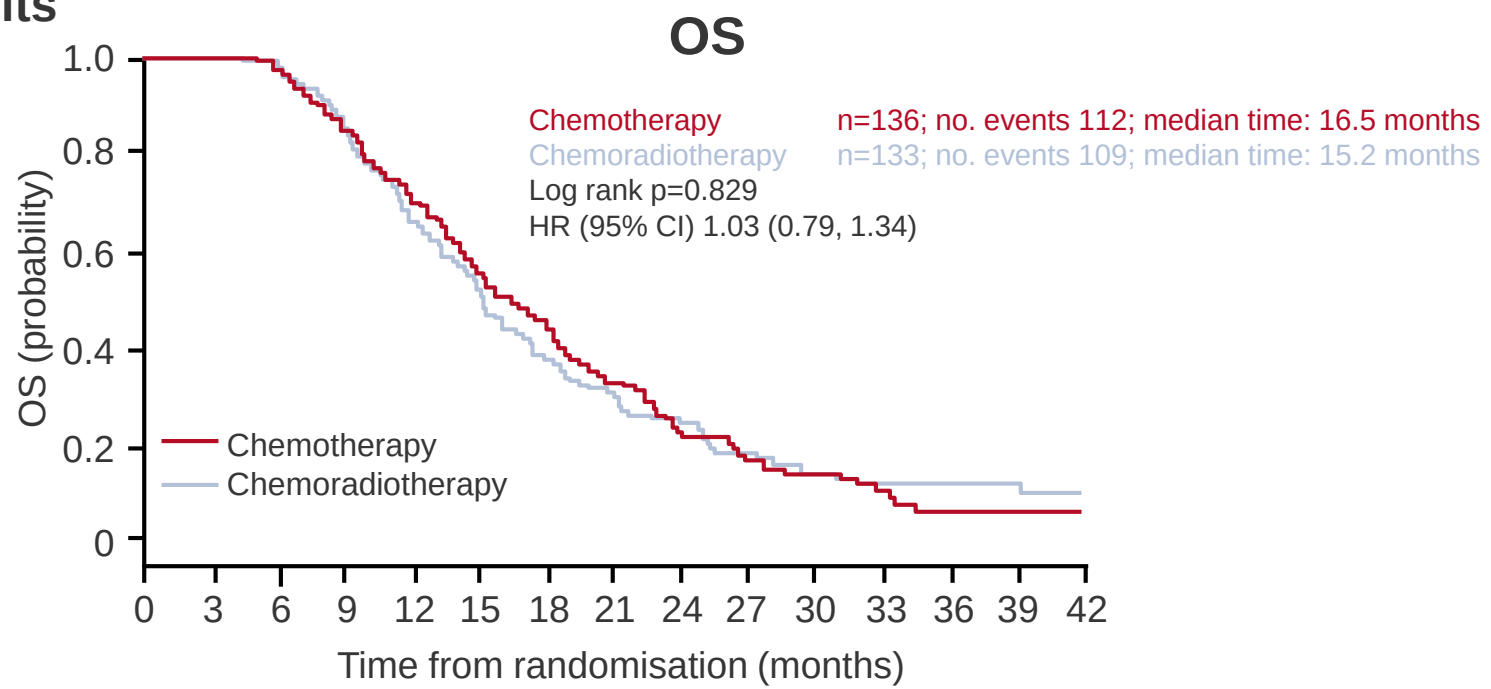
- PFS and tolerance

*1000 mg/m^2/wk x3; †100 mg/day; ‡54 Gy (5x 1.8 Gy/day) + capecitabine 1600 mg/m^2/day; ¥150 mg/day maintenance

Huguet et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4001)

4001: Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study – Huguet F et al

- **Key results**



- PFS: CT 8.4 mo vs CRT 9.9 mo; HR 0.78 (95% CI 0.61, 1.01); p=0.055
- Site of first progression (R2 patients):
  - Local/metastatic tumour progression: CT 46%/44% vs CRT 32%/60% (p=0.035)
- Time without treatment: CT 3.7 mo vs CRT 6.1 mo (p=0.017)

Huguet et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4001)

4001: Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study – Huguet F et al

- **Conclusions**
  - **OS was not improved in the CRT arm**
  - **There was a trend towards improved PFS and a longer period without treatment plus significantly less local tumour progression in the CRT arm, which could impact on the patients' quality of life**
  - **This study confirmed the value of frontline CT in patients with locally advanced pancreatic cancer to identify patients suitable for novel locoregional therapies**

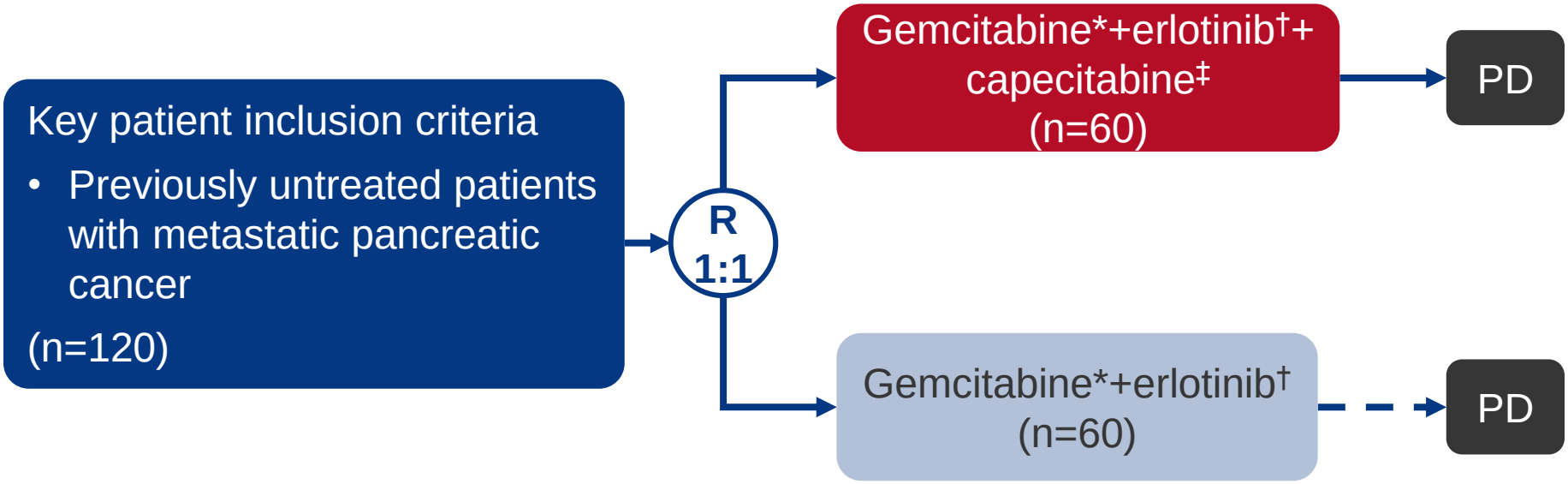
Huguet et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4001)

PANCREATIC CANCER

PALLIATIVE / METASTATIC

4122: Gemcitabine(G)/erlotinib(E) versus gemcitabine/erlotinib/capecitabine(C) in the first-line treatment of patients with metastatic pancreatic cancer (mPC): Efficacy and safety results of a phase IIb randomized study from the Spanish TTD Collaborative Group – Benavides M et al

- **Study objective**
  - To compare the efficacy and safety of gemcitabine/erlotinib/capecitabine (GEC) vs gemcitabine/erlotinib (GE) in the first-line treatment of patients with metastatic pancreatic cancer



Primary endpoint

- PFS

Secondary endpoints

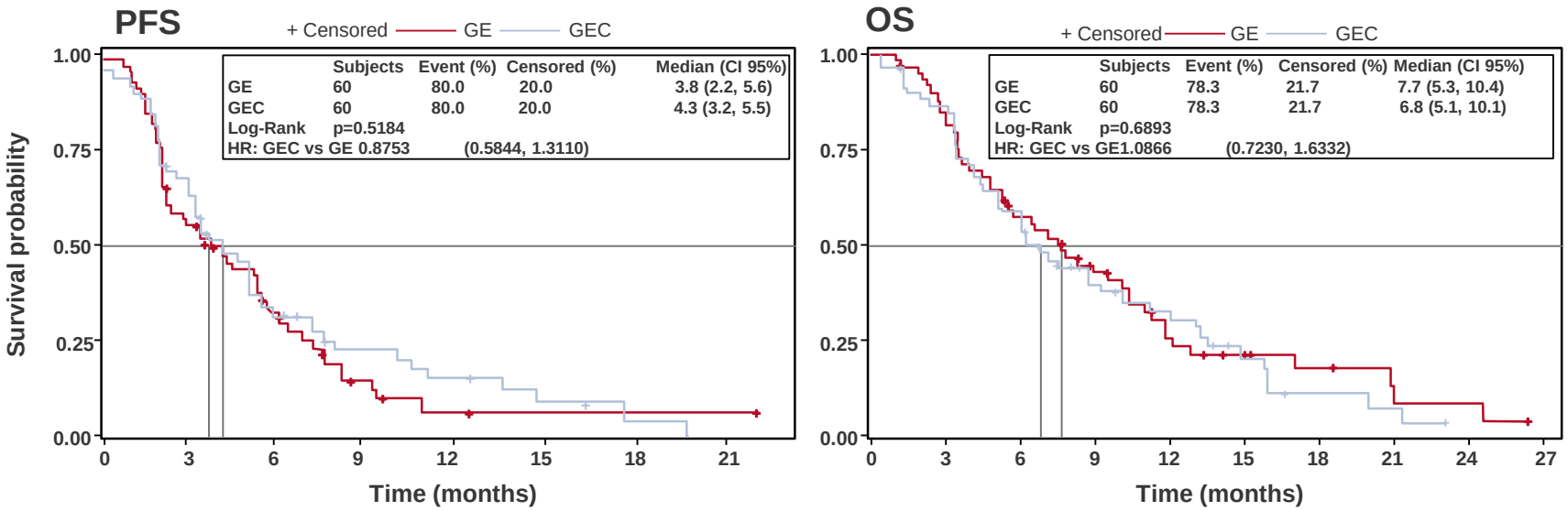
- OS, RR, relationship of rash with PFS/OS and safety

*1000 mg/m^2 days 1, 8, 15; †100 mg/day po; ‡830 mg/m^2/12h days 1–21

Benavides et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4122)

4122: Gemcitabine(G)/erlotinib(E) versus gemcitabine/erlotinib/capecitabine(C) in the first-line treatment of patients with metastatic pancreatic cancer (mPC): Efficacy and safety results of a phase IIb randomized study from the Spanish TTD Collaborative Group – Benavides M et al

- **Key results**

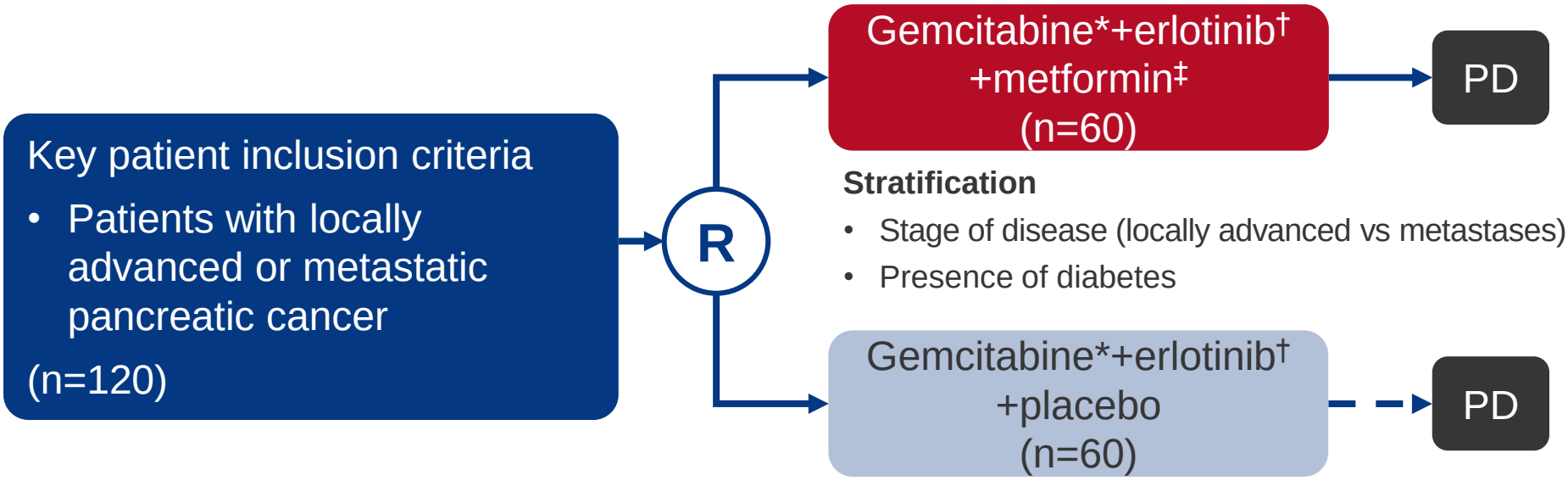


  - PFS and OS were significantly longer in patients with rash vs no rash (PFS: 5.5 vs 2.0 mo, HR 0.39 [95% CI 0.26, 0.6], p<0.0001; OS: 9.5 vs 4.0 mo, HR 0.51 [95% CI 0.33, 0.77], p=0.0014)
  - Treatment-related grade 3/4 AEs: 72% with GEC vs 55% with GE (p=0.0494)
- **Conclusions**
  - **Gemcitabine/erlotinib/capecitabine did not improve PFS compared with gemcitabine/erlotinib**
  - **Skin rash strongly predicted erlotinib efficacy, deserving further study**

Benavides et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4122)

4021: A phase II randomized, placebo controlled study to evaluate the efficacy of the combination of gemcitabine, erlotinib, and metformin in patients with locally advanced or metastatic pancreatic cancer – Wilmink J et al

- **Study objective**
  - To assess the efficacy of metformin vs placebo added to gemcitabine+erlotinib in patients with locally advanced or metastatic pancreatic cancer



Primary endpoint

- Survival at 6 months

Secondary endpoints

- OS, PFS, ORR, toxicity and PD

*1000 mg/m^2 on days 1, 8 and 15 q4w; †100 mg od;
‡500 mg bid in wk1, increased to 1000 mg bid if tolerated

Wilmink et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4021)

4021: A phase II randomized, placebo controlled study to evaluate the efficacy of the combination of gemcitabine, erlotinib, and metformin in patients with locally advanced or metastatic pancreatic cancer – Wilmink J et al

- **Key results**

	Placebo	Metformin	p
Survival at 6 mo, %	41.2	38.9	0.38
OS (95% CI), mo	7.6 (6.3, 9.0)	6.7 (5.1, 8.3)	0.52
PFS (95% CI), mo	5.4 (4.8, 6.1)	3.5 (1.1, 5.8)	0.44
ORR, %	8.9	9.1	0.61

  - Metformin was well tolerated with no significant differences in grade ≥3 toxicities between the two treatment groups

- **Conclusion**
  - **The addition of metformin to gemcitabine+erlotinib did not improve outcomes for patients with locally advanced or metastatic pancreatic cancer**

Wilmink et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4021)

4025: Phase II study of refametinib (BAY 86-9766), an allosteric dual MEK 1/2 inhibitor, and gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer – Van Laethem JL et al

- **Study objective**
  - To evaluate refametinib+gemcitabine in advanced pancreatic cancer

Key patient inclusion criteria
- Locally advanced, unresectable or metastatic pancreatic cancer
- ECOG PS ≤2
- No prior systemic therapy

(n=60)

→ Refametinib 50 mg bid po +gemcitabine* → PD

Primary endpoint
- ORR

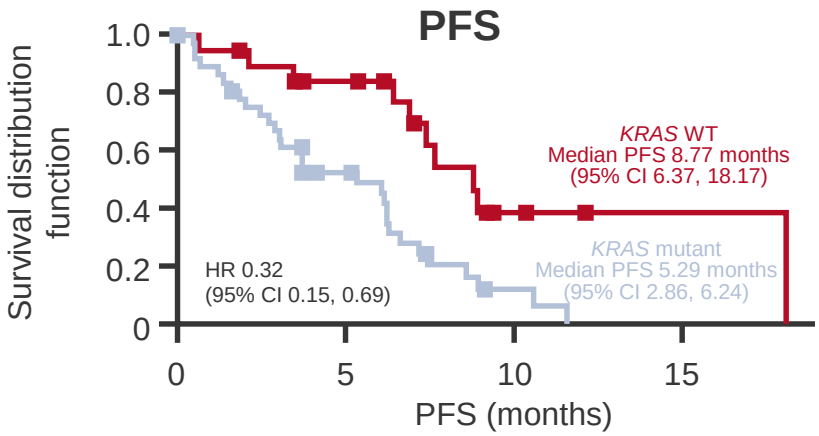
Secondary endpoints
- DOR, DCR, TTP, PFS, OS and safety

*1000 mg/m^2 IV weekly for 7 of 8 weeks in cycle 1, 3 of 4 weeks in subsequent cycles

Van Laethem et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4025)

4025: Phase II study of refametinib (BAY 86-9766), an allosteric dual MEK 1/2 inhibitor, and gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer – Van Laethem JL et al

- **Key results**
  - ORR: 28/48% (p=0.136), OS: 6.6/18.2 mo (HR 0.27 [95% CI 0.12, 0.62]) for mutant/wild-type, respectively



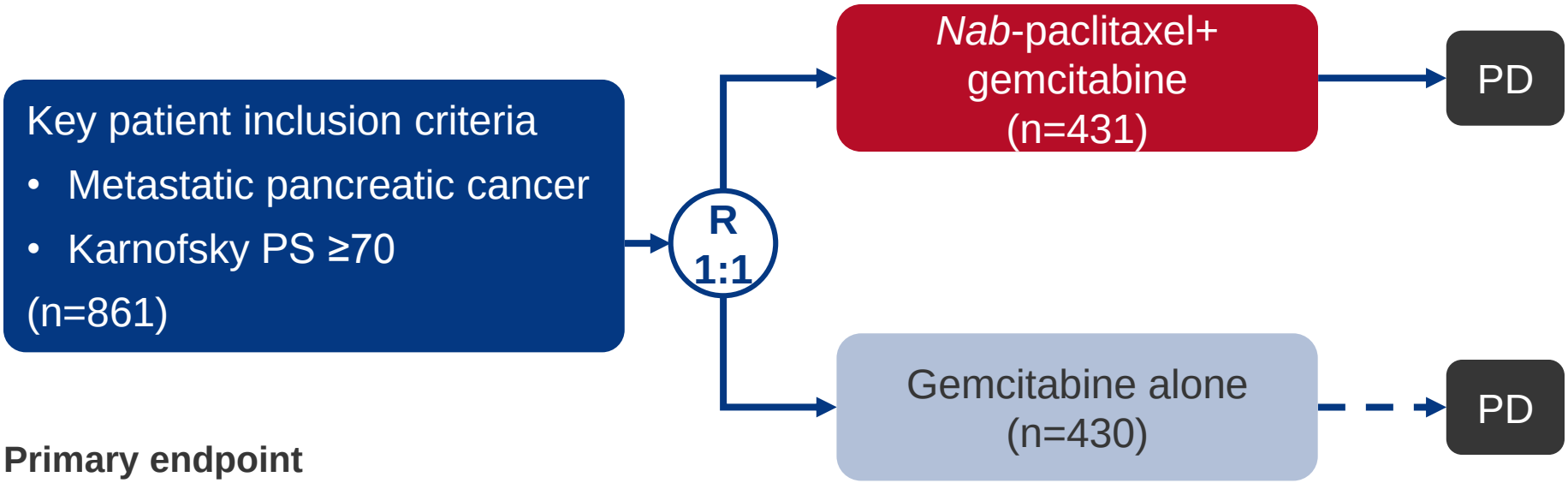
  - Most common grade 3/4 TEAEs were: neutropenia (43%), thrombocytopenia (22%), fatigues (15%), increased ALT (13%), anaemia (12%), hypertension (12%)

- **Conclusions**
  - **Refametinib+gemcitabine were active in patients with advanced pancreatic cancer, with an acceptable safety profile**
  - **There was a trend towards improved ORR, PFS and OS in *KRAS* wild-type patients**

Van Laethem et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4025)

4027: Analyses of updated overall survival (OS) and prognostic effect of neutrophil-to-lymphocyte ratio (NLR) and CA 19-9 from the phase III MPACT study of *nab*-paclitaxel (*nab*-P) plus gemcitabine (Gem) versus Gem for patients (pts) with metastatic pancreatic cancer – Goldstein D et al

- **Study objective**
  - *Post-hoc* analysis reporting updated OS data for the IMPACT trial, in which *nab*-paclitaxel+gemcitabine demonstrated superior OS vs gemcitabine alone in patients with metastatic pancreatic cancer



Primary endpoint

- OS

**nab*-P 125 mg/m^2 + gemcitabine 1000 mg/m^2 on days 1, 8, 15 of each 28-day cycle; †1000 mg/m^2 per wk for 7 wks, then 1 wk of rest (cycle 1), then days 1, 8, 15 of each 28-day cycle (cycle ≥2)

Goldstein et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4027)

4027: Analyses of updated overall survival (OS) and prognostic effect of neutrophil-to-lymphocyte ratio (NLR) and CA 19-9 from the phase III MPACT study of *nab*-paclitaxel (*nab*-P) plus gemcitabine (Gem) versus Gem for patients (pts) with metastatic pancreatic cancer – Goldstein D et al

- **Key results**
  - Median OS: 8.7 mo *nab*-P+gemcitabine vs 6.6 mo gemcitabine; HR 0.72 (95% CI 0.62, 0.83); p<0.001

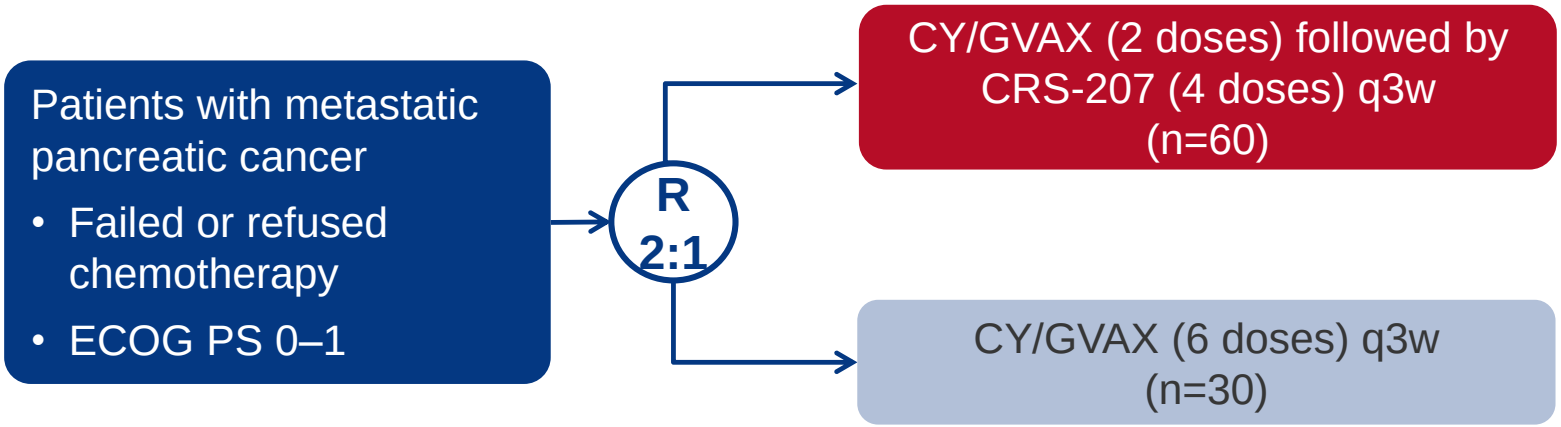
Multivariate analysis of OS		
Covariate	HR	p
nab-paclitaxel+gemcitabine vs gemcitabine	0.68 (0.57, 0.80)	<0.001
Liver metastases, yes vs no	1.65 (1.28, 2.12)	<0.001
KPS PS, 70–80 vs 90–100	1.47 (1.24, 1.74)	<0.001
NLR, ≤5 vs >5	0.57 (0.48, 0.68)	<0.001
Age, <65 vs ≥65 years	0.81 (0.69, 0.96)	0.016
Geographical region, Eastern Europe vs US	1.19 (0.99, 1.43)	0.063

- **Conclusion**
  - **Updated data confirmed the treatment effect favouring *nab*-paclitaxel+ gemcitabine vs gemcitabine alone for OS**

Goldstein et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4027)

177^: A phase 2, randomized trial of GVAX pancreas and CRS-207 immunotherapy versus GVAX alone in patients with metastatic pancreatic adenocarcinoma: Updated results – Le DT et al

- **Study objective**
  - To investigate the use of heterologous prime boost vaccinations in exploiting the immunostimulatory qualities of CY (cyclophosphamide; low dose)/GVAX pancreas (an irradiated whole-cell tumour vaccine) and CRS-207 (a live-attenuated double-deleted [LADD] *Listeria monocytogenes* vaccine expressing mesothelin)



Primary endpoint

- OS

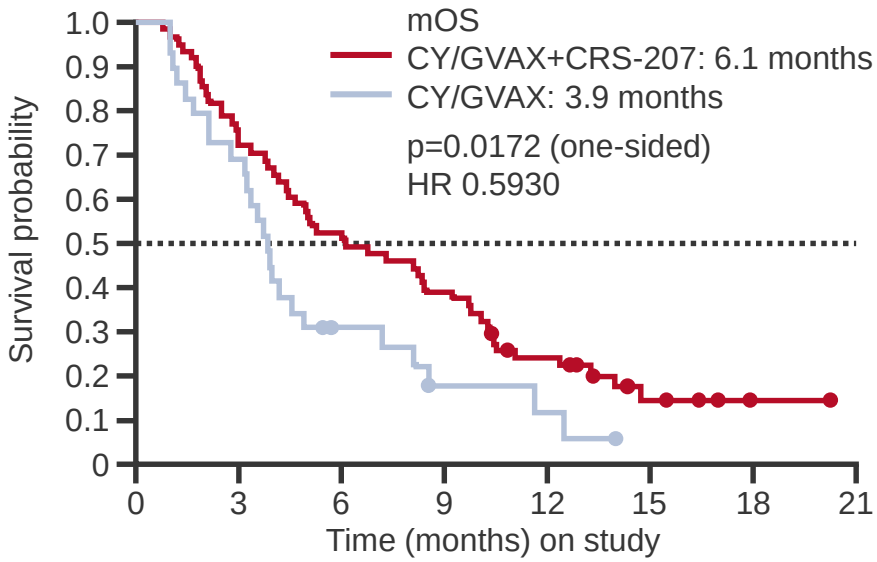
Secondary endpoints

- Safety, immune and clinical responses

Le et al. J Clin Oncol 2014; 32 (suppl 3; abstr 177^)

177^: A phase 2, randomized trial of GVAX pancreas and CRS-207 immunotherapy versus GVAX alone in patients with metastatic pancreatic adenocarcinoma: Updated results – Le DT et al

- **Key results**
  - CY/GVAX in combination with CRS-207 demonstrated improved median OS compared with CY/GVAX alone:



OS, mo	CY/GVAX+ CRS-207	CY/GVAX	HR	p-value
FAS interim analysis	6.0	3.4	0.4477	0.0057
FAS*	6.1	3.9	0.5930	0.0172
PP extended analysis‡	9.7	4.6	0.5290	0.0167
FAS 3rd-line treatment	5.7	3.7	0.2957	0.0003
PP 3rd-line treatment	8.3	4.0	0.2168	0.0002

  - 1-year survival probability for CY/GVAX in combination with CRS-207 was 24% compared with 12% for CY/GVAX alone
  - The only grade ≥3 related adverse event occurring in >5% of patients receiving CY/GVAX in combination with CRS-207 was lymphopenia (8.2% vs 3.4% for CY/GVAX alone)

*Received at least one dose; ‡Received at least 3 doses including 1 dose of CRS-207 Le et al. J Clin Oncol 2014; 32 (suppl 3; abstr 177^)

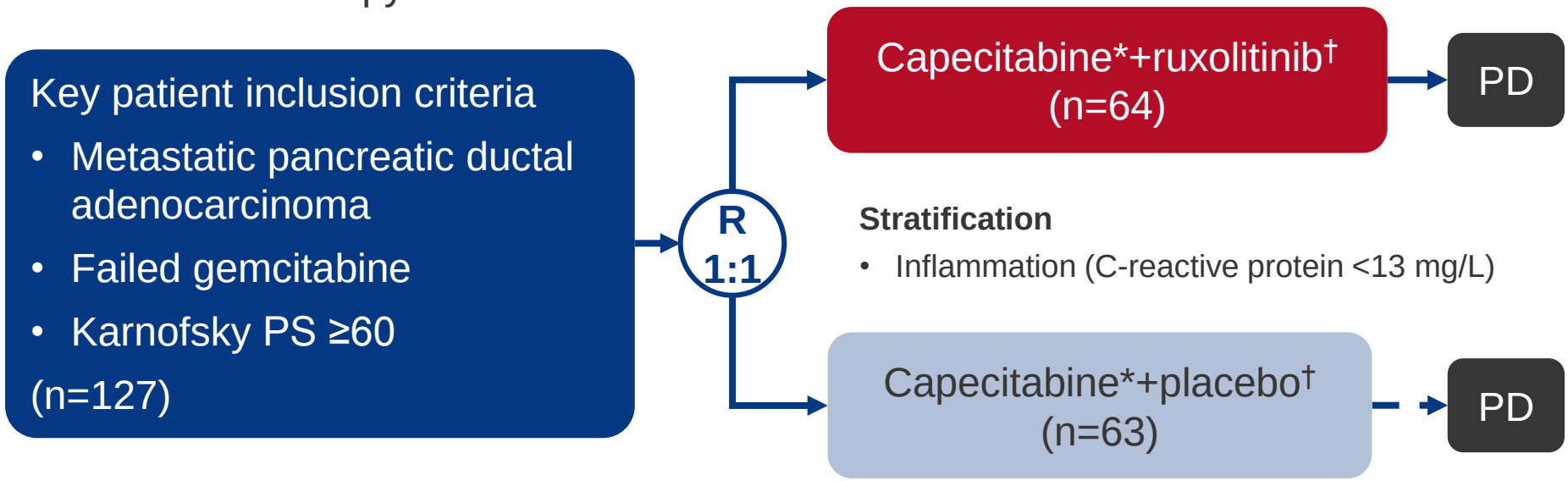
177^: A phase 2, randomized trial of GVAX pancreas and CRS-207 immunotherapy versus GVAX alone in patients with metastatic pancreatic adenocarcinoma: Updated results – Le DT et al

- **Conclusions**
  - **CY/GVAX in combination with CRS-207 demonstrated longer median OS than CY/GVAX alone in previously treated patients with metastatic pancreatic adenocarcinoma including those who received at least 3 doses**
  - **Both vaccines appeared to be safe and well tolerated**
  - **Additional studies of CY/GVAX in combination with CRS-207 are being conducted**

Le et al. J Clin Oncol 2014; 32 (suppl 3; abstr 177^)

4000: A randomized double-blind phase 2 study of ruxolitinib (RUX) or placebo (PBO) with capecitabine (CAPE) as second-line therapy in patients (pts) with metastatic pancreatic cancer (mPC) – Hurwitz H et al

- **Study objective**
  - To assess the efficacy and safety ruxolitinib (a JAK1/2 inhibitor that blocks pro-inflammatory cytokine-mediated signalling) added to capecitabine compared with capecitabine alone in patients with metastatic pancreatic cancer refractory to initial therapy



Primary endpoint

- OS

Secondary endpoints

- Clinical benefit response, ORR, PFS, confirmed response, QoL and safety

*1000 mg/m^2 bid days 1–14; †15 mg bid days 1–21

Hurwitz et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4000)

4000: A randomized double-blind phase 2 study of ruxolitinib (RUX) or placebo (PBO) with capecitabine (CAPE) as second-line therapy in patients (pts) with metastatic pancreatic cancer (mPC) – Hurwitz H et al

- **Key results**

	Ruxolitinib	Placebo	HR (95% CI)	p
Overall population	**N=64**	**N=63**		
Median OS, days	136.5	129.5	079 (0.53, 1.18)	0.25
Median PFS, days	51.0	46.0	0.75 (0.51, 1.10)	0.14
CRP >13 mg/L subgroup	**N=31**	**N=29**		
Median OS, days	83.0	55.0	0.47 (0.26, 0.85)	0.01
Median PFS, days	48.0	41.5	0.62 (0.35, 1.10)	0.10

	Ruxolitinib	Placebo
Overall population, n	**N=64**	**N=63**
Overall response (CR+PR)	5	1
Stable disease	21	22
Disease control (CR+PR+SD)	26	23
CRP >13 mg/L subgroup, n	**N=31**	**N=29**
Overall response (CR+PR)	2	1
Stable disease	9	5
Disease control (CR+PR+SD)	11	6

Hurwitz et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4000)

4000: A randomized double-blind phase 2 study of ruxolitinib (RUX) or placebo (PBO) with capecitabine (CAPE) as second-line therapy in patients (pts) with metastatic pancreatic cancer (mPC) – Hurwitz H et al

- **Key results**

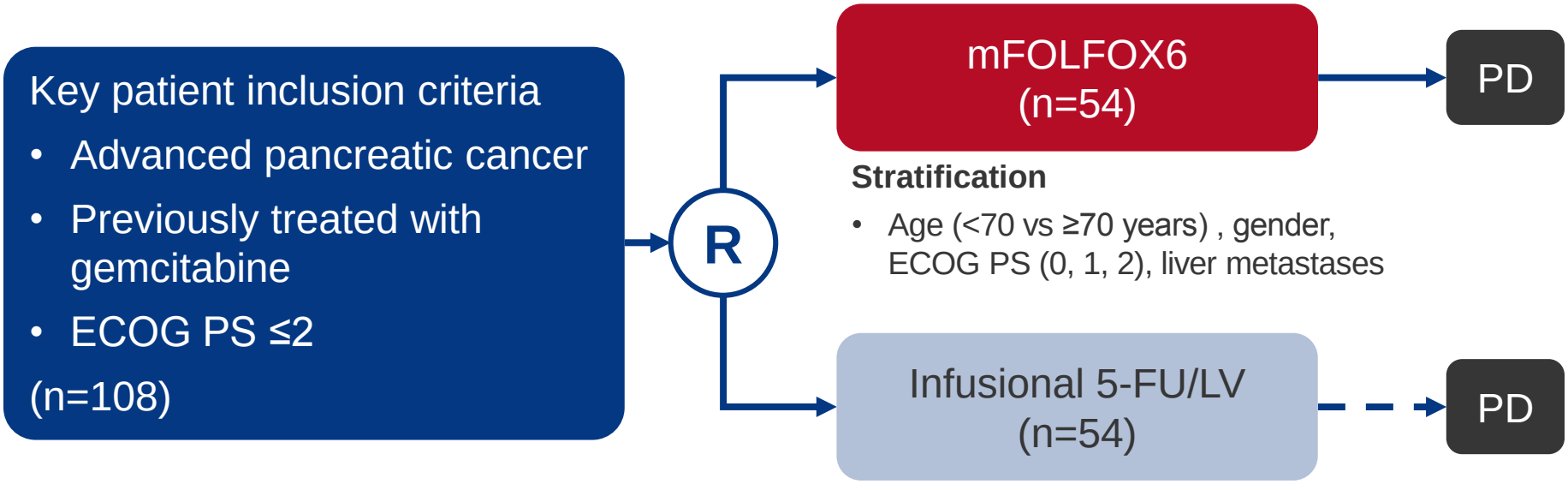
AEs	Ruxolitinib (N=59)	Placebo (N=60)
Mean exposure, days	**99.6**	**67.4**
Any AE, n (%)	58 (98.3)	60 (100)
Grade ≥3 AE, n (%)	44 (74.6)	49 (81.7)
Discontinued treatment due to AE, n (%)	7 (11.9)	12 (20.0)
Grade 3/4 haematological AE, n (%)		
Anaemia	9 (15.3)	1 (1.7)
Thrombocytopenia	1 (1.7)	2 (3.3)
Neutropenia	0	1 (1.7)

- **Conclusions**
  - **Ruxolitinib in combination with capecitabine exhibited clinical activity in patients with metastatic pancreatic cancer**
  - **Ruxolitinib appeared to improve survival in patients with inflammation**
  - **Ruxolitinib was generally well tolerated**

Hurwitz et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4000)

4022: PANCREOX: A randomized phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients (pts) who have received gemcitabine (GEM)-based chemotherapy (CT) – Gill S et al

- **Study objective**
  - To evaluate the benefit of mFOLFOX6 vs infusional 5-FU/LV in patients with advanced pancreatic cancer



Primary endpoint

- PFS

Secondary endpoints

- ORR, OS, QoL and safety

Gill et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4022)

4022: PANCREOX: A randomized phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients (pts) who have received gemcitabine (GEM)-based chemotherapy (CT) – Gill S et al

- **Key results**

Variable	mFOLFOX6	5-FU/LV	HR (95% CI)	p
Median age, years	65	67		0.40
Stage (%)				
Locally advanced	7.4	5.6		0.68
Metastatic	92.6	94.4		
Median PFS, mo	3.1	2.9	1.00 (0.66, 1.53)	0.989
Median OS, mo	6.1	9.9	1.78 (1.08, 2.93)	0.24
ORR, %	13.2	8.5		0.36
EORTC-QLQ-C30*, mo	2.2	3.8	1.37 (0.73, 2.57)	0.33

  - Grade 3/4 AEs: 63% with mFOLFOX6 vs 11% with 5-FU/LV
  - Withdrawal rate due to AE: 16.3% with mFOLFOX6 vs 1.9% with 5-FU/LV
- **Conclusions**
  - **PFS was similar and OS was inferior with mFOLFOX6 vs 5-FU/LV**
  - **The findings suggest that oxaliplatin-based CT should primarily be used as 1st-line treatment**

*Time to definite deterioration >10 patients

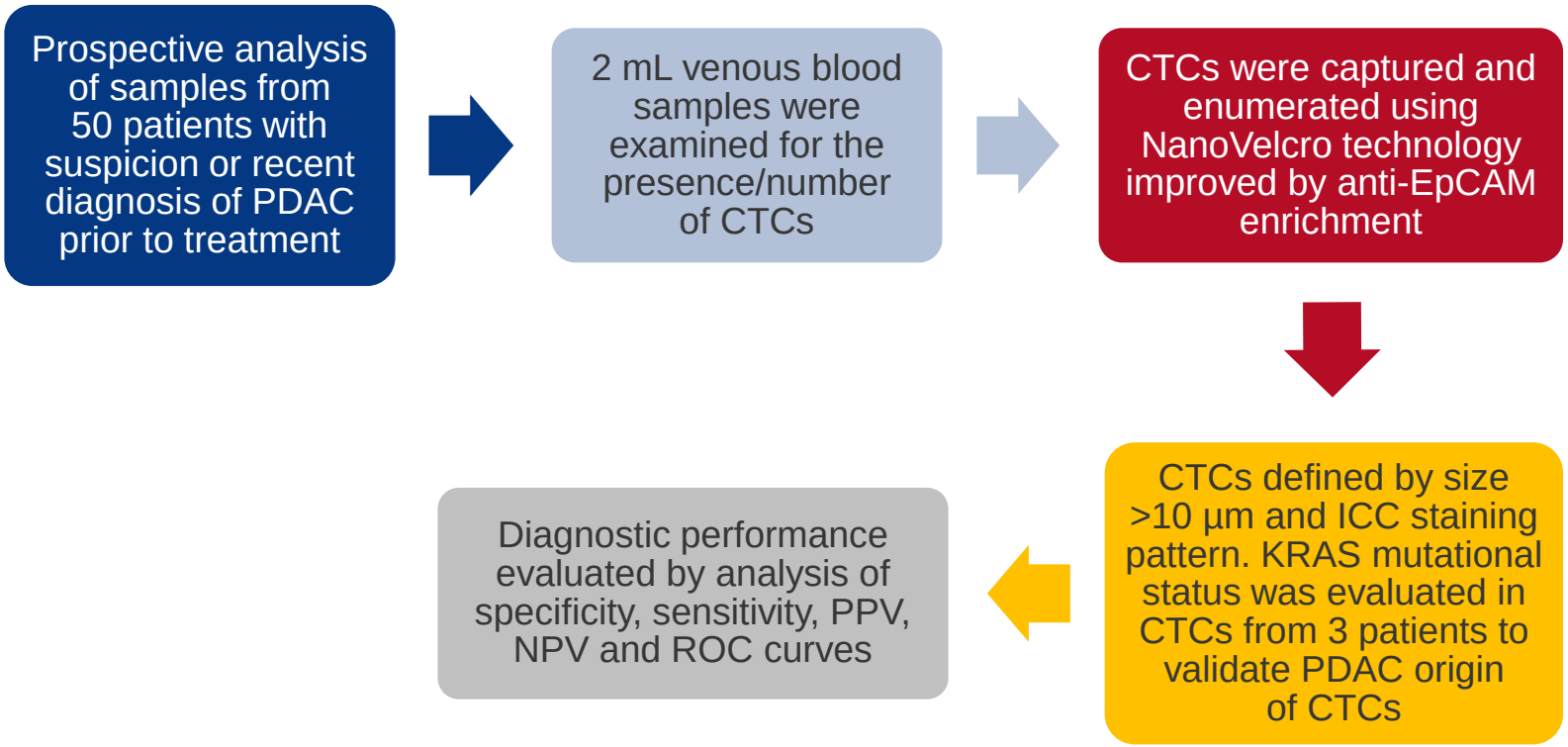
Gill et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4022)

PANCREATIC CANCER

BIOMARKERS

175: Pancreatic circulating tumor cells as a diagnostic adjunct in pancreatic cancer – Ankeny JS et al

- **Study objective**
  - To investigate the use of circulating tumour cells (CTCs) as a potential diagnostic biomarker in pancreatic ductal adenocarcinoma (PDAC)



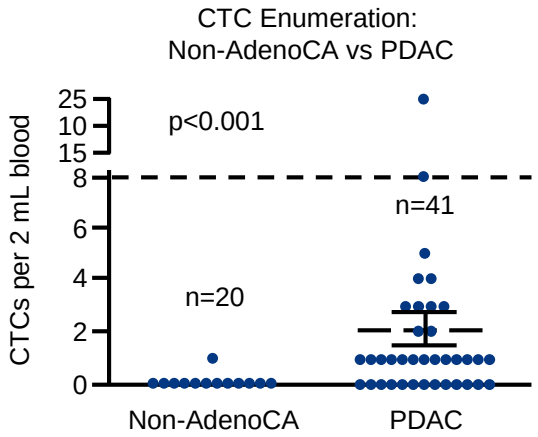
Ankeny et al. J Clin Oncol 2014; 32 (suppl 3; abstr 175)

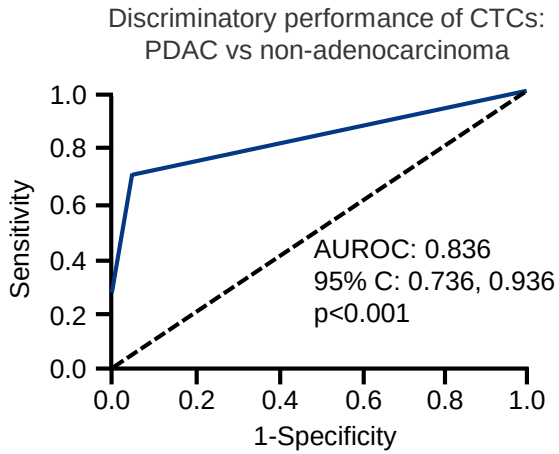
175: Pancreatic circulating tumor cells as a diagnostic adjunct in pancreatic cancer – Ankeny JS et al

- **Key results**
  - Presence of CTCs allowed PDAC to be distinguished from non-adenocarcinoma:

Diagnostic parameters at various CTC cut-off values

CTC cut-off	Sensitivity	Specificity	PPV	NPV	Youden's index
≥ 1 CTC	***0.707***	***0.950***	***0.967***	***0.594***	***0.637***
≥ 2 CTC	0.293	1.000	1.000	0.408	0.293
≥ 4 CTC	0.146	1.000	1.000	0.377	0.146
≥ 5 CTC	0.098	1.000	1.000	0.357	0.098
≥ 10 CTC	0.024	1.000	1.000	0.339	0.024





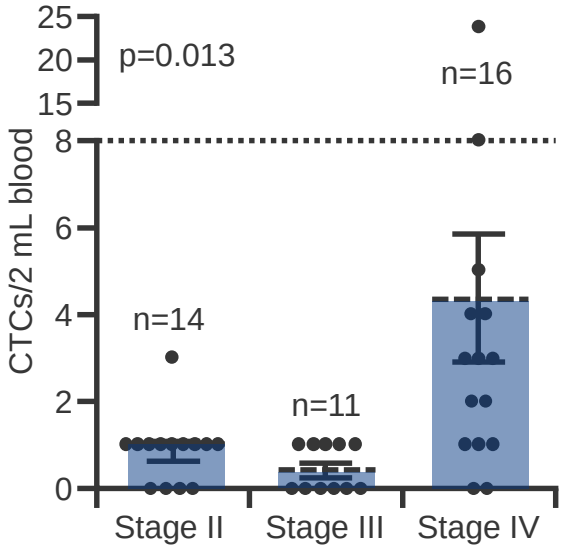
CTC, circulating tumour cell; PDAC, pancreatic ductal adenocarcinoma

Ankeny et al. J Clin Oncol 2014; 32 (suppl 3; abstr 175)

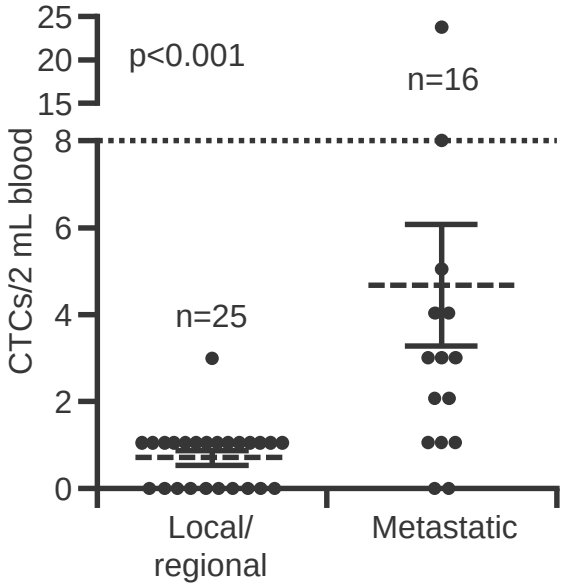
175: Pancreatic circulating tumor cells as a diagnostic adjunct in pancreatic cancer – Ankeny JS et al

- **Key results**
  - Presence of CTCs allowed local disease to be distinguished from metastatic disease, at a cut-off of ≥2 CTCs/2 mL blood, sensitivity = 68.8%, specificity = 96.0% and PPV = 92.3%:

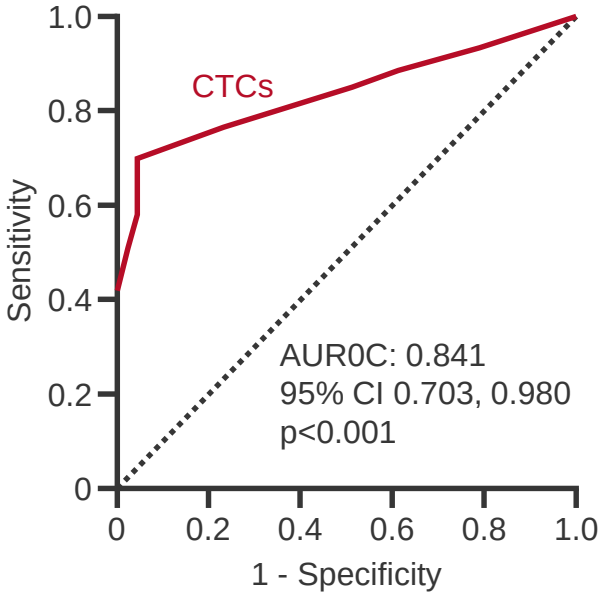
CTC enumeration: PDAC stage



CTC enumeration: Local/regional vs metastatic



Discriminatory performance of CTCs: Local/regional vs metastatic PDAC



CTC, circulating tumour cell; PDAC, pancreatic ductal adenocarcinoma; PPV, positive predictive value

Ankeny et al. J Clin Oncol 2014; 32 (suppl 3; abstr 175)

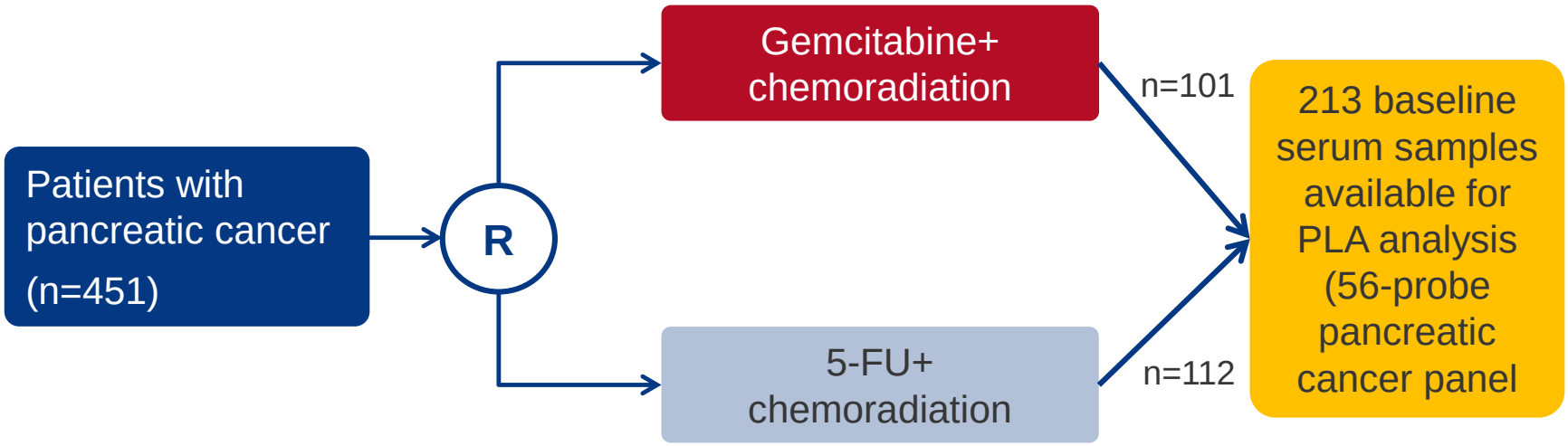
175: Pancreatic circulating tumor cells as a diagnostic adjunct in pancreatic cancer – Ankeny JS et al

- **Conclusions**
  - **When diagnosing PDAC, CTCs may be a useful biomarker**
  - **CTCs were shown to have high specificity and PPV for distinguishing between local and metastatic disease in patients with PDAC**
  - **The use of CTCs as a diagnostic biomarker may allow for improved pre-treatment staging at the time of disease presentation**

Ankeny et al. J Clin Oncol 2014; 32 (suppl 3; abstr 175)

176: A novel biomarker panel examining response to adjuvant pancreatic cancer therapy in RTOG 9704 – Heestand GM et al

- **Study objective**
  - To determine whether a biomarker signature when using a proximity ligation assay (PLA) panel can predict response to adjuvant therapy in pancreatic cancer



Primary endpoints

- OS, DFS

Heestand et al. J Clin Oncol 2014; 32 (suppl 3; abstr 176)

176: A novel biomarker panel examining response to adjuvant pancreatic cancer therapy in RTOG 9704 – Heestand GM et al

- **Key results**
  - Univariate survival analysis demonstrated that improved OS in all patients was associated with reduced levels of CEA and CA 19-9:

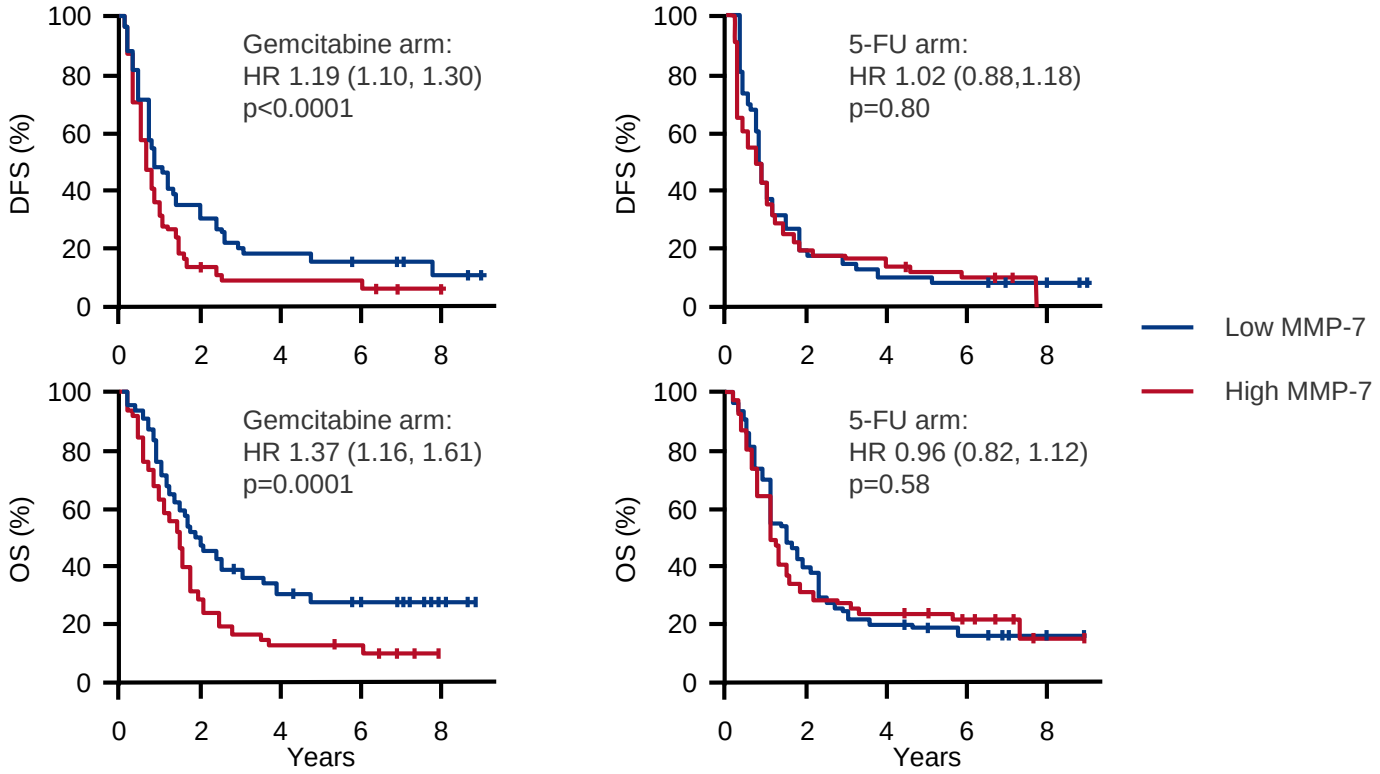
	All Patients	5-FU	Gemcitabine
CA 19-9	1.20 (1.11, 1.30)* p<0.0001	1.20 (1.08, 1.33)* p<0.0001	1.21 (1.06, 1.39)* p<0.0001
CEA	1.19 (1.04, 1.38)* p<0.0001	1.43 (1.12, 1.83)* p<0.0001	1.12 (0.90, 1.38) p=0.094
MMP-7	1.15 (0.98, 1.34) p=0.0054	0.96 (0.73, 1.25) p=0.58	1.39 (1.05, 1.83)* p=0.0001

*Significance was maintained with multivariate analysis

Heestand et al. J Clin Oncol 2014; 32 (suppl 3; abstr 176)

176: A novel biomarker panel examining response to adjuvant pancreatic cancer therapy in RTOG 9704 – Heestand GM et al

- **Key results**
  - Low levels of MMP-7 were associated with significant improvement in disease-free survival and OS in the patients receiving adjuvant therapy compared with high levels; this was not observed in patients receiving 5-FU



Gemcitabine arm: MMP-7 < median: MST 1.99 years; MMP-7 ≥ median: MST 1.52 years

MMP-7, matrix metalloproteinase-7; MST, median survival time

Heestand et al. J Clin Oncol 2014; 32 (suppl 3; abstr 176)

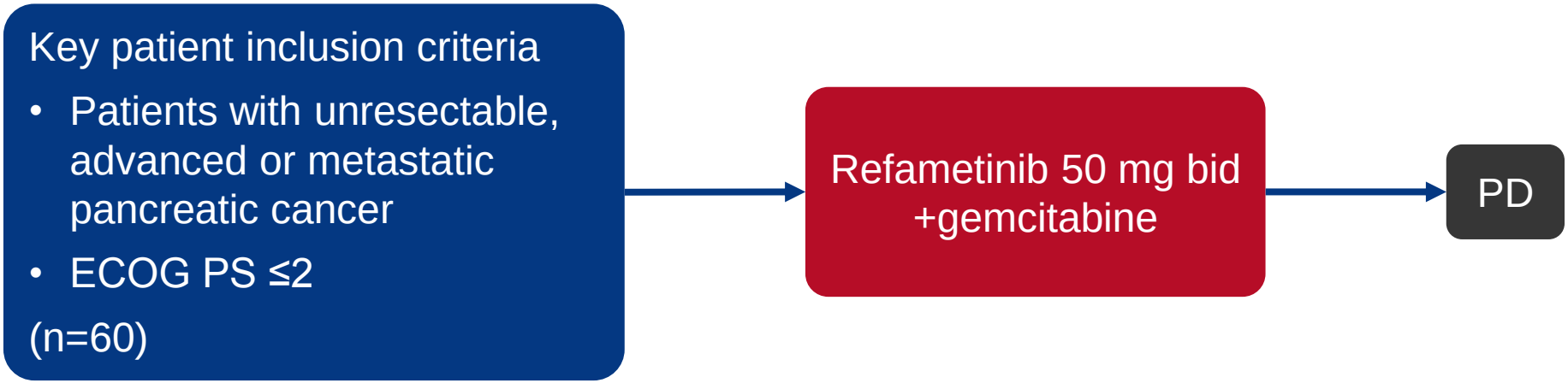
176: A novel biomarker panel examining response to adjuvant pancreatic cancer therapy in RTOG 9704 – Heestand GM et al

- **Conclusions**
  - **PLA was demonstrated to be a useful tool for identifying potential biomarkers from archived serum samples**
  - **The findings also suggest that MMP-7 levels may be used as a predictor for patient response to adjuvant gemcitabine**

Heestand et al. J Clin Oncol 2014; 32 (suppl 3; abstr 176)

4129: Phase II study of the MEK inhibitor refametinib (BAY 86-9766) in combination with gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer: Biomarker results – Riess H et al

- **Study objective**
  - Biomarker analysis to assess the relationship between *KRAS* mutation and treatment response in patients with advanced pancreatic cancer receiving refametinib+gemcitabine



Primary endpoint

- ORR

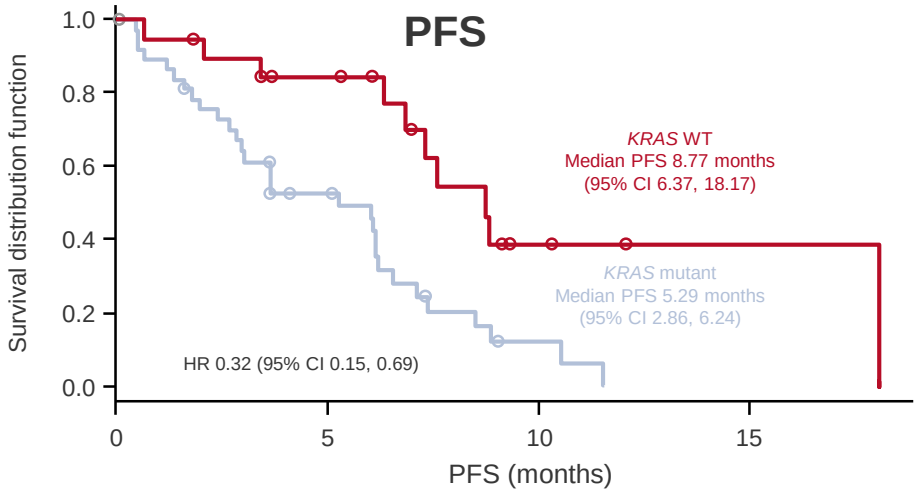
Secondary endpoints

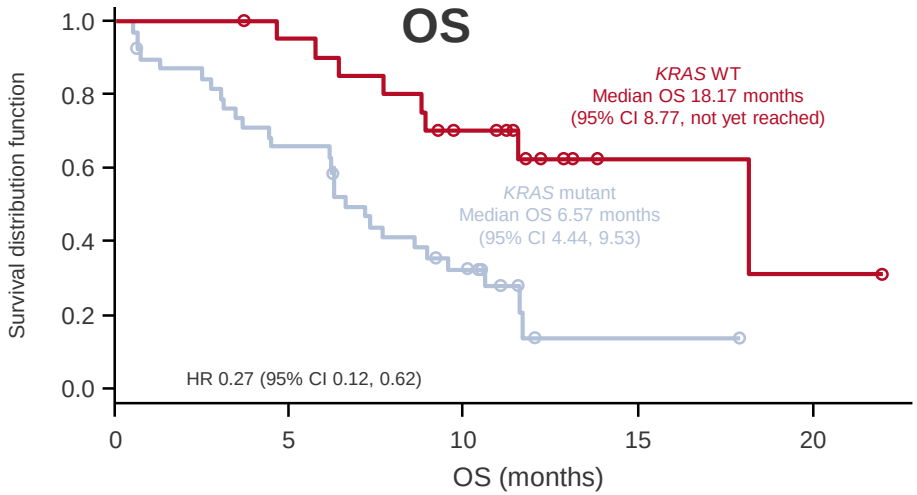
- PFS, OS and biomarker assessment

Reiss et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4129)

4129: Phase II study of the MEK inhibitor refametinib (BAY 86-9766) in combination with gemcitabine in patients with unresectable, locally advanced, or metastatic pancreatic cancer: Biomarker results – Riess H et al

- **Key results**
  - *KRAS* mutation status: wild-type n=21, mutant n=39
  - ORR (at least unconfirmed PR): wild-type 48% vs mutant 28% (p=0.136)





  - There was a trend correlating allele frequency with response:
    - *KRAS* mutant allele frequency: PR 1.51 (SD 1.36)
- **Conclusion**
  - **There was a trend towards improved response, median PFS and OS in the *KRAS* wild-type subset and for *KRAS* allele frequency to correlate with response**

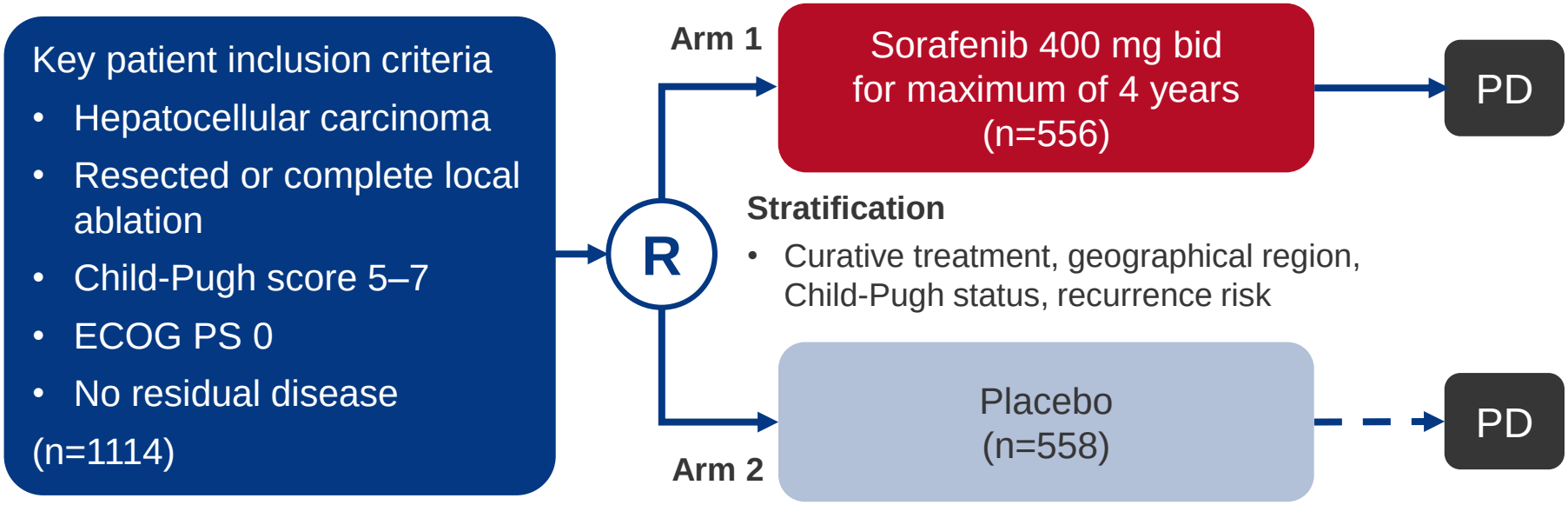
Reiss et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4129)

HEPATOCELLULAR CARCINOMA

ADJUVANT THERAPY

4006: STORM: A phase III randomized, double-blind, placebo-controlled trial of adjuvant sorafenib after resection or ablation to prevent recurrence of hepatocellular carcinoma (HCC) – Bruix J et al

- **Study objective**
  - To evaluate the efficacy and safety of adjuvant sorafenib in patients with hepatocellular carcinoma



Primary endpoint

- Recurrence-free survival

Secondary endpoints

- Time to recurrence, OS, PROs, PK and biomarkers

Bruix et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4006)

4006: STORM: A phase III randomized, double-blind, placebo-controlled trial of adjuvant sorafenib after resection or ablation to prevent recurrence of hepatocellular carcinoma (HCC) – Bruix J et al

- **Key results**
  - No differences in recurrence-free survival, time to recurrence or OS were observed with sorafenib

	Sorafenib (n=558)	Placebo (n=558)	HR (95% CI)	p-value*
Median, months				
RFS	33.4	33.8	0.94 (0.78, 1.13)	0.26
TTR	38.6	35.8	0.89 (0.74, 1.08)	0.12
OS	NR	NR	0.99 (0.76, 1.30)	0.48

  - Discontinuation rates with sorafenib were higher due to AEs (24% vs 7%) and withdrawal of consent (17% vs 6%)

*One-sided; NR, not reached

Bruix et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4006)

4006: STORM: A phase III randomized, double-blind, placebo-controlled trial of adjuvant sorafenib after resection or ablation to prevent recurrence of hepatocellular carcinoma (HCC) – Bruix J et al

- **Key results**

TEAEs, n (%)	Sorafenib (n=559)	Placebo (n=548)
All	545 (97.5)	491 (89.6)
Serious	225 (40.3)	228 (41.6)
Grade 5	15 (2.7)	9 (1.6)
Leading to dose modification	439 (78.5)	111 (20.3)
Leading to permanent discontinuation	147 (26.3)	59 (10.8)

- **Conclusions**
  - **The primary endpoint of the trial (RFS) was not met and there were also no improvements in time to recurrence or OS**
  - **AEs were consistent with the known safety profile of sorafenib**
  - **Sorafenib is not recommended in the adjuvant treatment of HCC**

*One-sided; NR, not reached

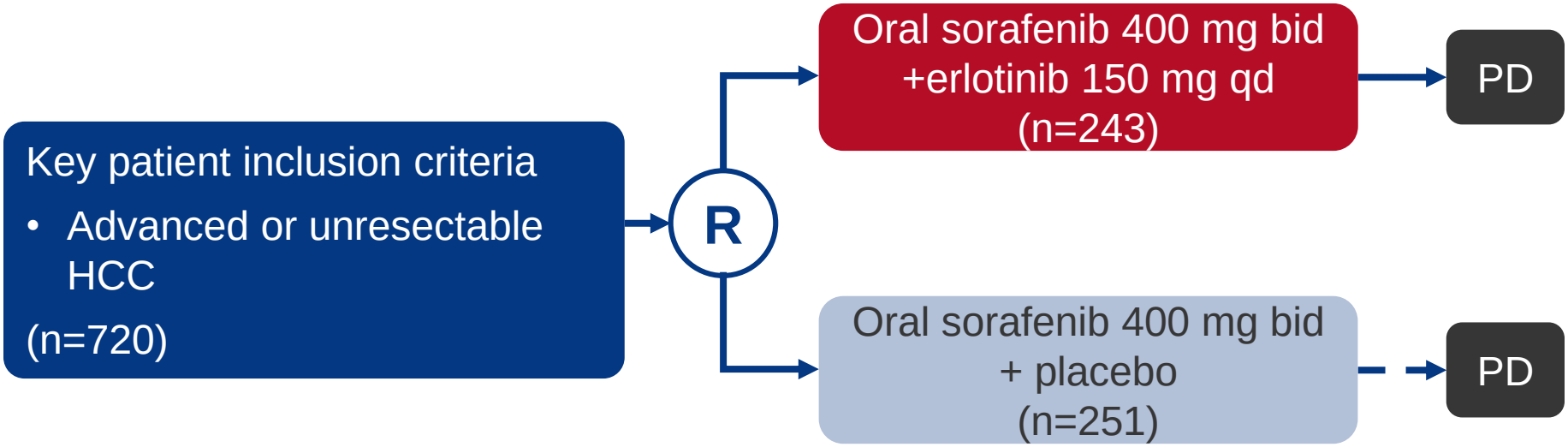
Bruix et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4006)

HEPATOCELLULAR CARCINOMA

BIOMARKERS

4028: Biomarker analyses and association with clinical outcomes in patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib with or without erlotinib in the phase III SEARCH trial – Zhu AX et al

- **Study objective**
  - To identify biomarkers predicting prognosis and/or response to sorafenib±erlotinib in patients with advanced HCC from the SEARCH trial



  - The following biomarkers were analysed in baseline plasma samples:
    - VEGF-A, VEGF-C, PDGF-BB, KIT (extracellular domain), HGF, bFGF, IGF-2, amphiregulin, betacellulin, EGF, epigen, epiregulin, heregulin, hbEGF, TGF-α
  - Mutations in 19 oncogenes were analysed in archival biopsies

Zhu et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4028)

4028: Biomarker analyses and association with clinical outcomes in patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib with or without erlotinib in the phase III SEARCH trial – Zhu AX et al

- **Key results**
  - High HGF and VEGF-A baseline plasma levels were associated with poorer outcomes; high KIT and VEGF-C were associated with better outcomes

Poorer outcome		
	Low	High
HGF n Median OS (95% CI)	212 12.4 (10.7, 13.8)	282 7.5 (6.5, 8.5)
HR (95% CI); p-value	1.67 (1.35, 2.07); 5e-05	
VEGF-A n Median OS (95% CI)	284 12.4 (10.5, 12.0)	210 7.6 (6.3, 9.4)
HR (95% CI); p-value	1.39 (1.12, 1.70); p=0.03	

Better outcome		
	Low	High
KIT n Median OS (95% CI)	339 8.7 (7.4, 10.3)	155 10.6 (8.3, 12.9)
HR (95% CI); p-value	0.71 (0.56, 0.90); p=0.05	
VEGF-C n Median TTP (95% CI)	239 2.7 (2.6, 2.9)	255 4.4 (4.0, 5.5)
HR (95% CI)	0.62 (0.49, 0.77); 3e-04	

- **Conclusions**
  - **HGF, VEGF-A, KIT and VEGF-C baseline plasma levels were linked with clinical outcomes in HCC patients treated with sorafenib+erlotinib**
  - **These biomarkers plus epigen constituted a multi-marker composite signature for improved OS**

*Low vs high expression. Adj, multiplicity adjusted

Zhu et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4028)

CHOLANGIOCARCINOMA & GALLBLADDER CANCER

ADJUVANT THERAPY

4030: SWOG S0809: A phase II trial of adjuvant capecitabine (cap)/gemcitabine (gem) followed by concurrent capecitabine and radiotherapy in extrahepatic cholangiocarcinoma (EHCC) and gallbladder carcinoma (GBCA) – Ben-Josef E et al

- **Study objective**
  - To evaluate the role of adjuvant therapy after resection of EHCC or GBCA

Key patient inclusion criteria
- EHCC or GBCA s/p radical resection
- pT2-4, N1 or R1
- M0 and PS 0-1

→ **Gemcitabine** 4 cycles (1 g/m^2 IV, days 1, 8) + **capecitabine** (1500 mg/m^2/day, days 1–14) q3w, then concurrent **CAP** (1330 mg/m^2/day) + radiation (n=79) → PD

Stratification
- R0 or R1
- EHCC or GBCA

Primary endpoint
- OS

Secondary endpoints
- DFS and safety

EHCC, extrahepatic cholangiocarcinoma;
GBCA, gallbladder carcinoma

Ben-Josef et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4030)

4030: SWOG S0809: A phase II trial of adjuvant capecitabine (cap)/gemcitabine (gem) followed by concurrent capecitabine and radiotherapy in extrahepatic cholangiocarcinoma (EHCC) and gallbladder carcinoma (GBCA) – Ben-Josef E et al

- **Key results**
  - R0 n=54 vs R1 n=25; 62% EHCC vs 38% GBCA
  - Grade 3/4 AEs were observed in 53/11% of patients, respectively
    - Most common: neutropenia (44%), hand-foot syndrome (13%), diarrhoea (8%), lymphopenia (8%) and leukopenia (6%)
  - Median OS was 33 months (33/30 for R0/R1)

% (95% CI)	All pts	R0 cohort	R1 cohort	EHCC	GBCA
2-year OS	62 (50, 72)	65 (51, 77)	56 (33, 74)	66 (50, 78)	56 (37, 72)
2-year DFS	50 (38, 60)	52 (38, 65)	44 (23, 63)	51 (36, 65)	47 (28, 63)
2-year LR	12 (5, 19)	10 (2, 18)	18 (2, 33)	11 (2, 21)	13 (1, 25)

- **Conclusions**
  - **This trial established the feasibility of adjuvant treatment in EHCC and GBCA**
  - **Efficacy data and completion rate are promising and warrant further study**

EHCC, extrahepatic cholangiocarcinoma;
GBCA, gallbladder carcinoma

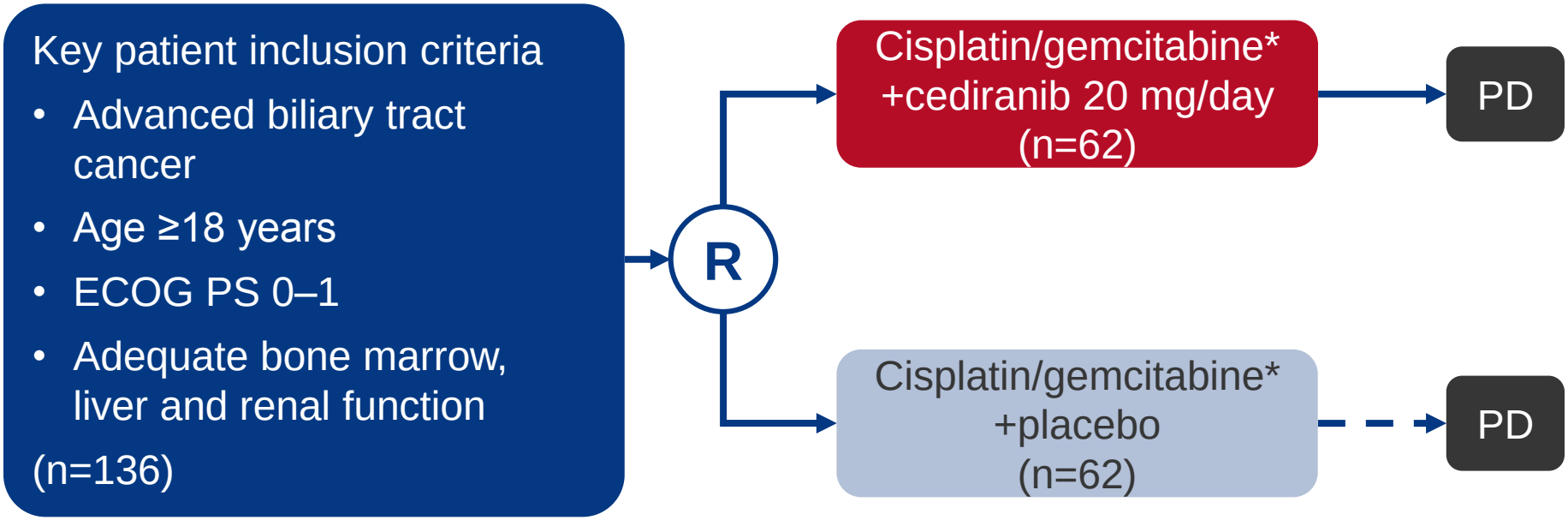
Ben-Josef et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4030)

BILIARY TRACT CANCER

PALLIATIVE / METASTATIC

4002: ABC-03: A randomized phase II trial of cediranib (AZD2171) or placebo in combination with cisplatin/gemcitabine (CisGem) chemotherapy for patients (pts) with advanced biliary tract cancer (ABC) – Valle JW et al

- **Study objective**
  - To determine whether combining cediranib (a pan-VEGF receptor TKI with some activity against PDGF receptors and c-Kit) with cisplatin/gemcitabine compared with cisplatin/gemcitabine alone improves outcomes in patients with advanced biliary tract cancer



Primary endpoint

- PFS

Secondary endpoints

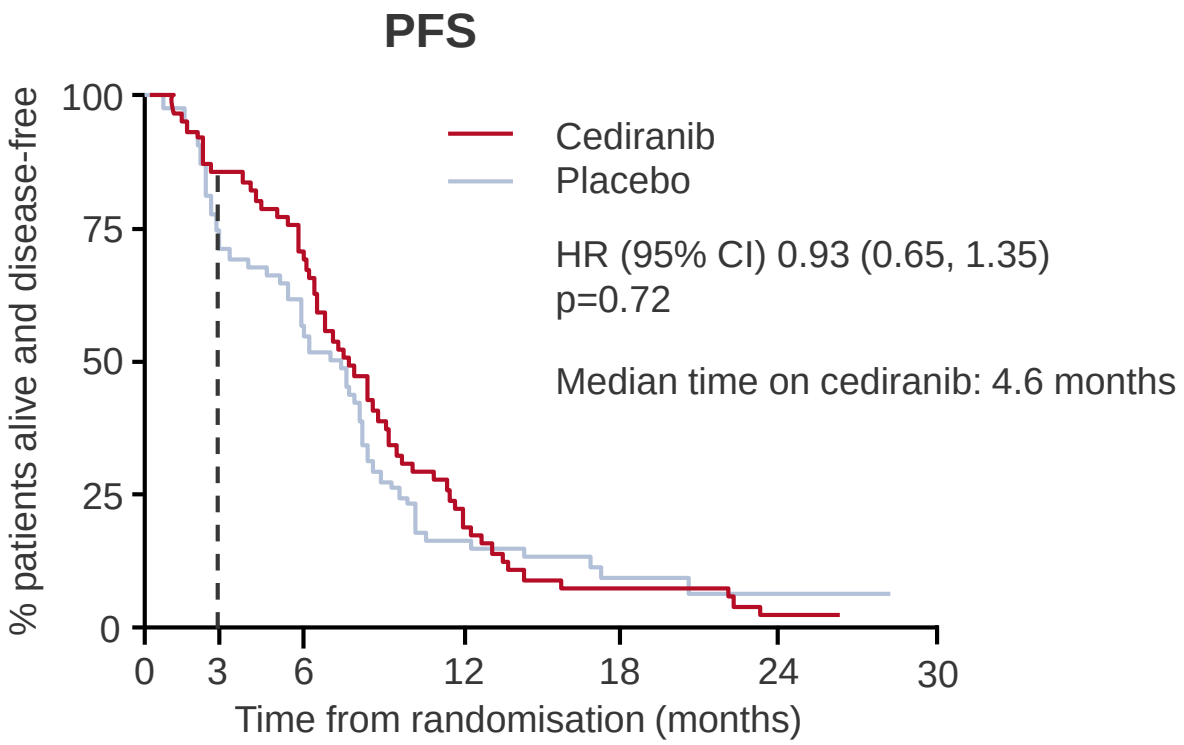
- OS, ORR (RECIST v1.1), toxicity and QoL

Cisplatin (25 mg/m^2) + gemcitabine (1000 mg/m^2) days 1 and 8 of a 21-day cycle (up to 8 cycles)

Valle et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4002)

4002: ABC-03: A randomized phase II trial of cediranib (AZD2171) or placebo in combination with cisplatin/gemcitabine (CisGem) chemotherapy for patients (pts) with advanced biliary tract cancer (ABC) – Valle JW et al

- **Key results**



  - ORR: 44% with cediranib vs 19% with placebo, p=0.0036
  - Median OS: 14.1 mo with cediranib vs 11.9 mo with placebo (HR 0.86 [95% CI 0.58, 1.27]; p=0.44)

Valle et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4002)

4002: ABC-03: A randomized phase II trial of cediranib (AZD2171) or placebo in combination with cisplatin/gemcitabine (CisGem) chemotherapy for patients (pts) with advanced biliary tract cancer (ABC) – Valle JW et al

- **Key results**

Biomarker	Categories	HR (95% CI)	p-value
CA19-9	<37.0	1.0	0.001
	≥37 to <492	1.0 (0.6, 1.7)	
	≥492	2.3 (1.4, 3.9)	
CA125	<20	1.0	0.001
	≥20 to <61	1.0 (0.6, 1.7)	
	≥61	2.4 (1.4, 3.9)	
CEA	<3.2	1.0	0.03
	≥3.2 to <8.0	1.4 (0.8, 2.3)	
	≥8.0	1.9 (1.2, 3.2)	

  - Patients with high (≥7515 pg/mL) vs medium (5523–7514 pg/mL)/low (<5522 pg/mL) baseline VEGFR2 levels had a shorter OS (HR 1.8 [95% CI 1.0, 3.2]; p=0.04)

Grade 3–4 AEs, n (%)	Cediranib	Placebo	p-value
Haematological	32 (52)	28 (45)	0.47
Non-haematological	55 (89)	46 (74)	0.04

- **Conclusions**
  - **Cediranib did not increase PFS but appeared to improve the response rate**
  - **Cediranib was associated with an increase in grade 3–4 toxicities**
  - **Current and future biomarker data may reveal the potential for selecting patients most likely to benefit in future studies**

Valle et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4002)

OESOPHAGEAL & GASTRIC CANCER

OESOPHAGEAL & GASTRIC CANCER

CURATIVE INTENT: SURGERY & OTHER MODALITIES

05: The effect of postoperative morbidity on survival after resection for gastric adenocarcinoma: Results from the U.S. Gastric Cancer Collaborative – Jin LX et al

- **Study objective**
  - A retrospective analysis to evaluate the impact of postoperative complications on survival after resection for gastric adenocarcinoma
- **Study design**
  - Data were collected for 965 patients between 1/1/2000 and 31/12/2012 from seven US Gastric Cancer Collaborative centres
  - In total, data from 850 patients with non-metastatic gastric or GEJ adenocarcinoma who underwent complete gross resection were analysed

Jin et al. J Clin Oncol 2014; 32 (suppl 3; abstr 05)

05: The effect of postoperative morbidity on survival after resection for gastric adenocarcinoma: Results from the U.S. Gastric Cancer Collaborative – Jin LX et al

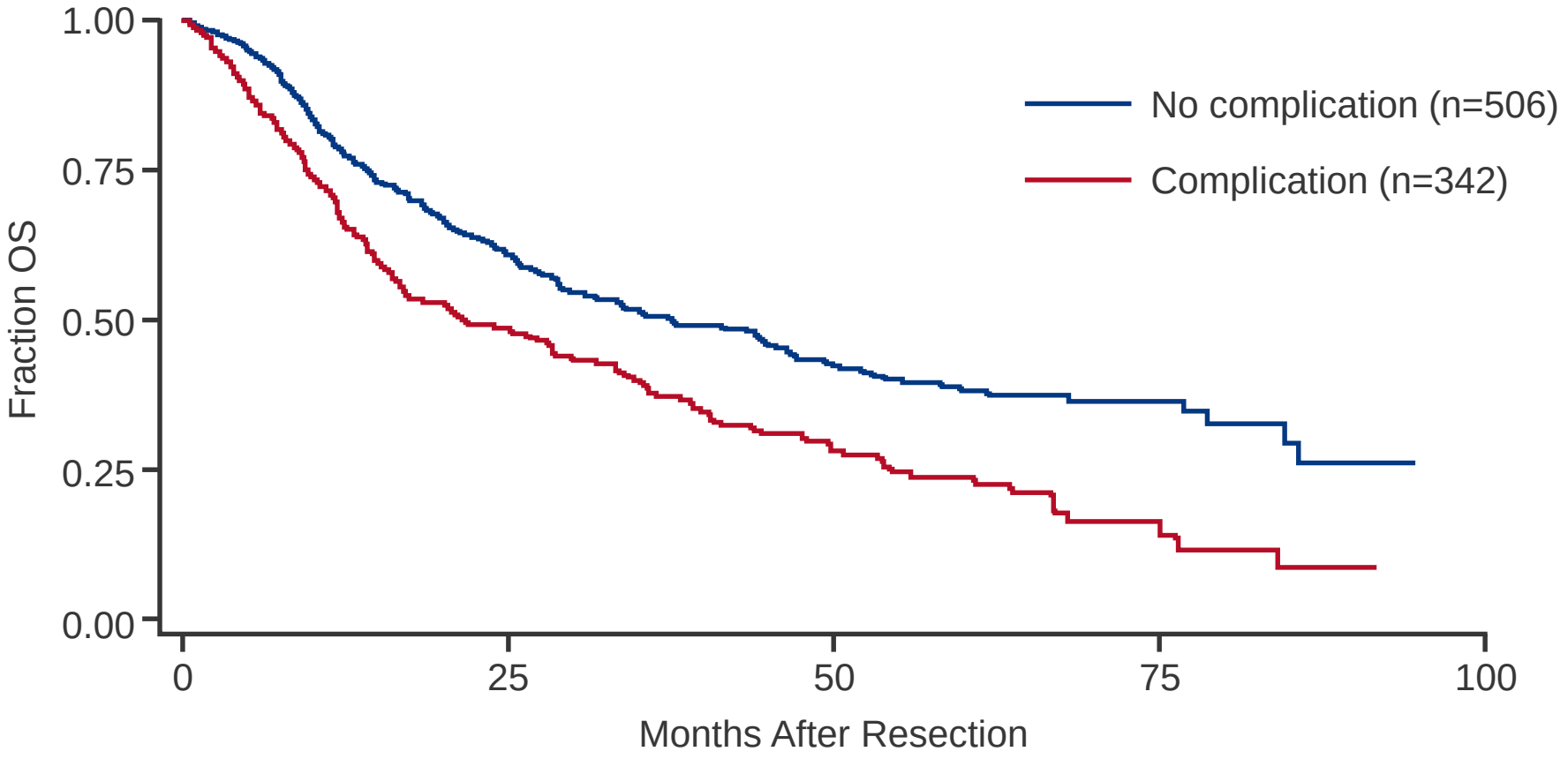
- **Key results**
  - The following factors were found to be associated with survival:

Significant variables	Median OS (mo)	Overall Survival (OS) Univariate p-value	Multivariate p-value	HR (95% CI)
Neoadjuvant therapy				
Yes (n=174)	24	0.012	0.01	1.7 (1.1, 2.6)
No (n=675)	38			
Perineural invasion				
Yes (n=202)	15	<0.0001	0.02	1.6 (1.1, 2.5)
No (n=426)	47			
AJCC stage (7th edition)				
Stage 3 or 4 (n=445)	18	<0.0001	0.02	1.8 (1.1, 2.9)
Stage 1 or 2 (n=405)	68			
Post-operative complications				
Yes (n=342)	25	<0.0001	0.004	1.6 (1.1, 2.4)
No (n=506)	45			

Jin et al. J Clin Oncol 2014; 32 (suppl 3; abstr 05)

05: The effect of postoperative morbidity on survival after resection for gastric adenocarcinoma: Results from the U.S. Gastric Cancer Collaborative – Jin LX et al

- **Key results**
  - OS was significantly longer ($p<0.001$) in patients with no complications compared with patients with complications:



Jin et al. J Clin Oncol 2014; 32 (suppl 3; abstr 05)

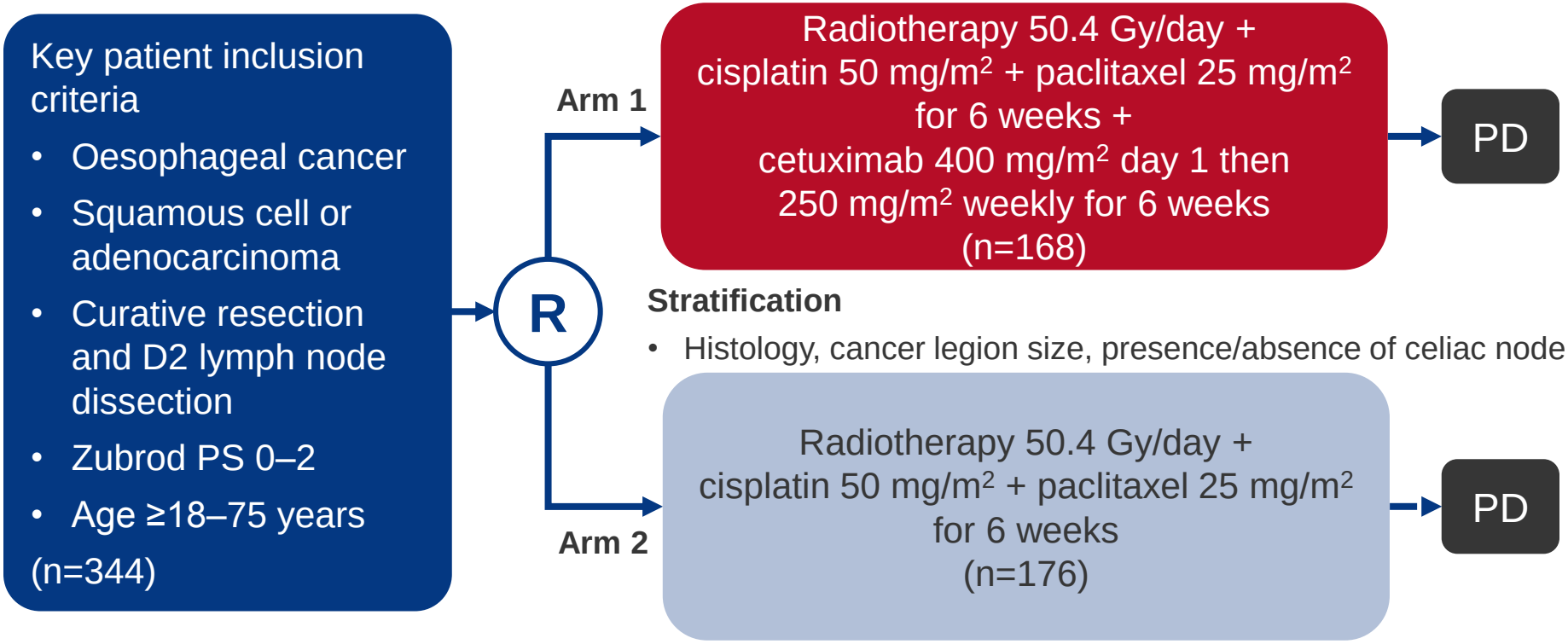
05: The effect of postoperative morbidity on survival after resection for gastric adenocarcinoma: Results from the U.S. Gastric Cancer Collaborative – Jin LX et al

- **Conclusions**
  - **Overall 40% of patients who had surgery for gastric adenocarcinoma suffered from complications**
  - **Complications were not increased by neoadjuvant therapy**
  - **Adjuvant therapy was less likely to be used in patients suffering from complications (48% vs. 60%)**
  - **Overall survival was decreased in patients with complications (25 vs. 45 months, HR=1.6)**

Jin et al. J Clin Oncol 2014; 32 (suppl 3; abstr 05)

4007: RTOG 0436: A phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery – Ilson DH et al

- **Study objective**
  - To evaluate the addition of cetuximab to concurrent chemoradiation compared with chemoradiation alone in patients with inoperable oesophageal carcinoma



Primary endpoint

- OS

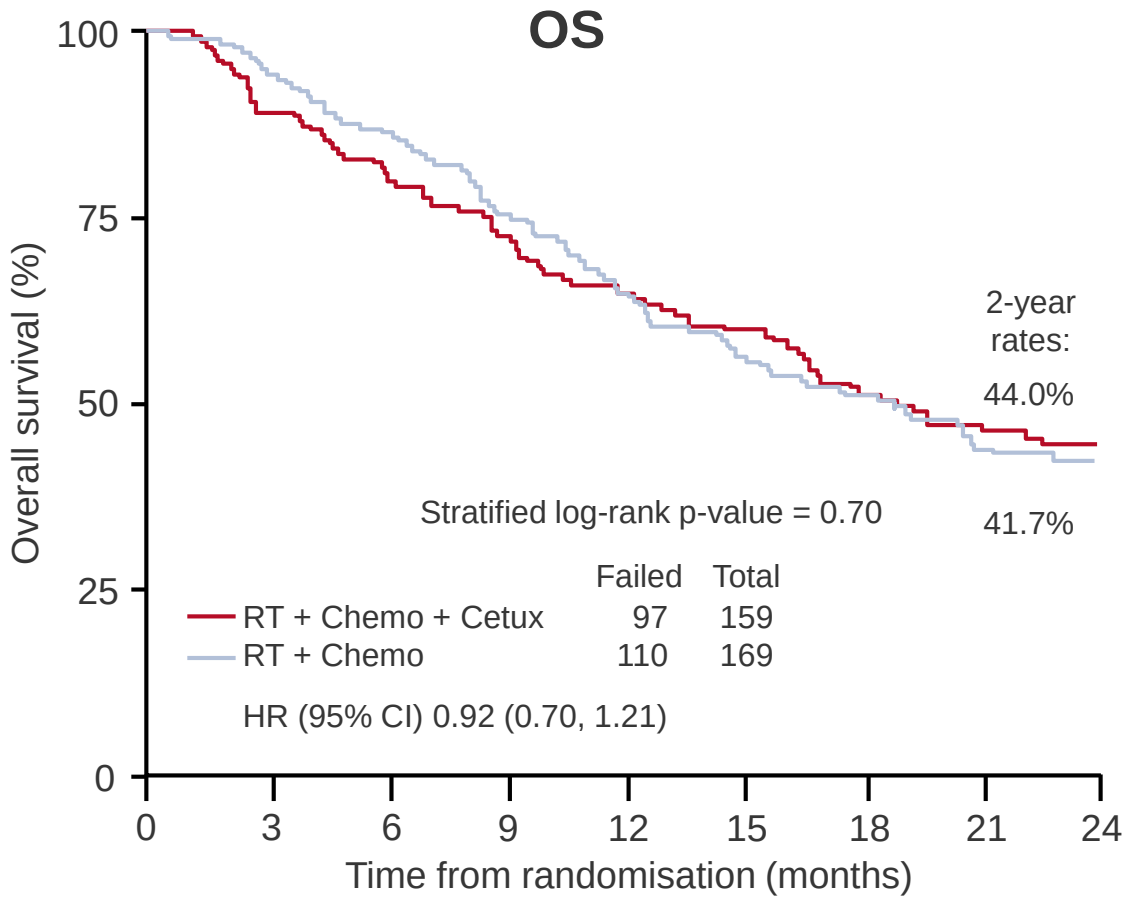
Secondary endpoints

- Complete clinical response, safety and QoL

Ilson et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4007)

4007: RTOG 0436: A phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery – Ilson DH et al

- **Key results**



Ilson et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4007)

4007: RTOG 0436: A phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery – Ilson DH et al

- **Key results**

AEs, n (%)	RT+CT+cetuximab (N=157)	RT+CT (N=169)
Worse non-haematological		
Grade 3	71 (45)	76 (45)
Grade 4	21 (13)	11 (7)
Worse haematological		
Grade 3	71 (45)	83 (49)
Grade 4	35 (22)	28 (17)

- **Conclusions**
  - **The addition of cetuximab to chemoradiation did not improve OS in patients with inoperable oesophageal carcinoma**
  - **A number of studies indicate that there is no benefit of current EGFR-targeted agents in unselected patients with this cancer type**

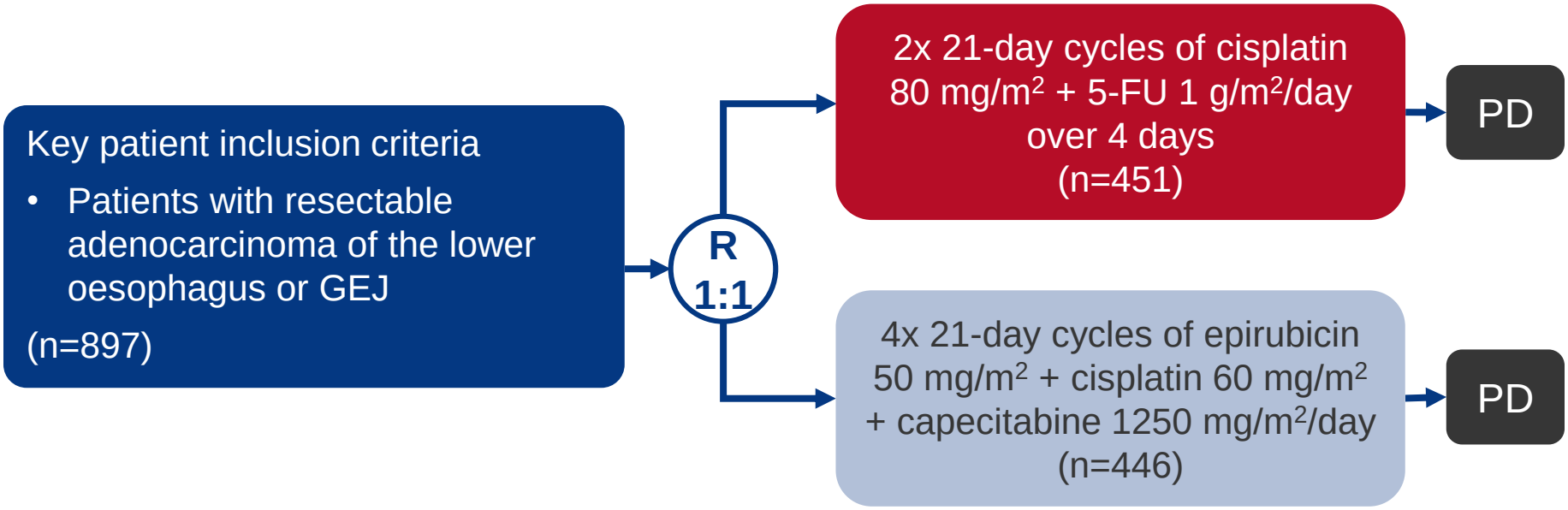
Ilson et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4007)

OESOPHAGEAL & GASTRIC CANCER

NEOADJUVANT & ADJUVANT THERAPY

4014: Toxicity, surgical complications, and short-term mortality in a randomized trial of neoadjuvant cisplatin/5FU versus epirubicin/cisplatin and capecitabine prior to resection of lower esophageal/gastroesophageal junction (GOJ) adenocarcinoma (MRC OEO5, ISRCTN01852072, CRUK 02/010) – Cunningham D et al

- **Study objective**
  - To compare CF vs ECX pre-operatively, followed by oesophagectomy in patients with resectable adenocarcinoma of the lower oesophagus or GEJ



Primary endpoint

- OS (not yet reported)

Secondary endpoints

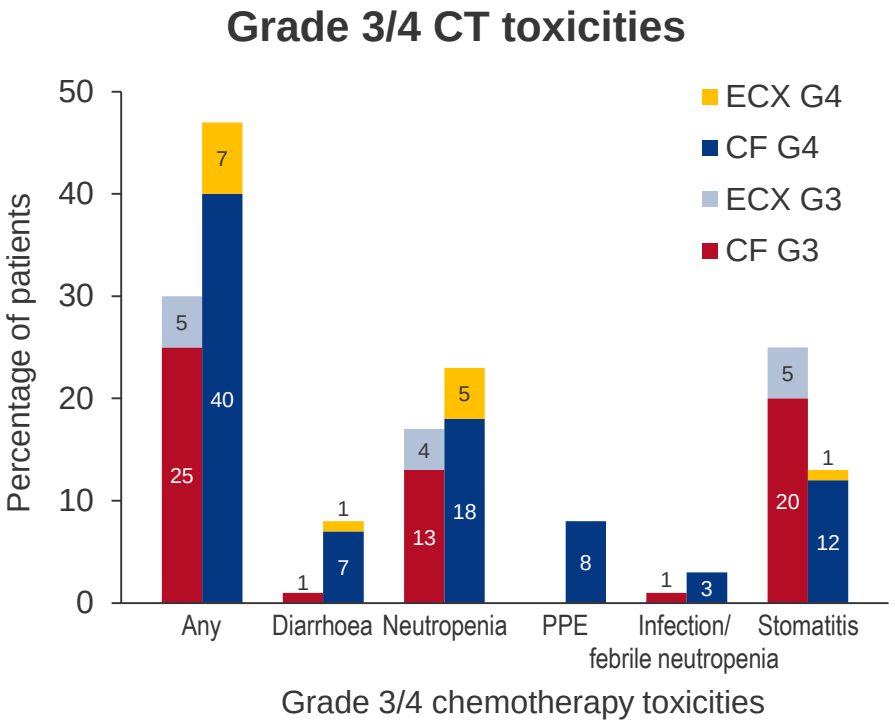
- Toxicity and mortality

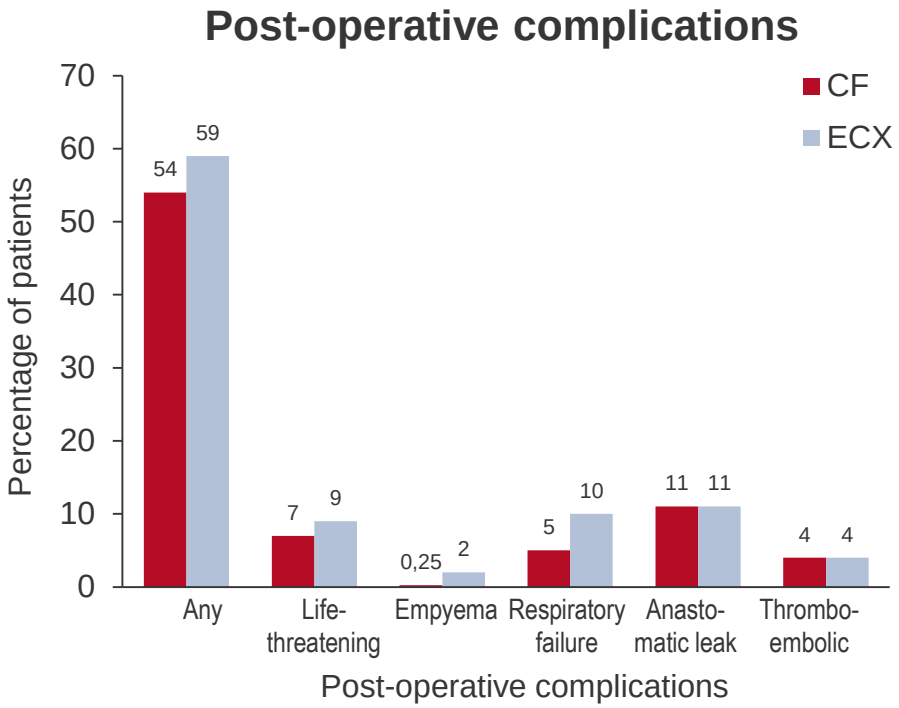
CF, cisplatin/5-FU; ECX, epirubicin/cisplatin+capecitabine; GEJ, gastro-oesophageal junction

Cunningham et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4014)

4014: Toxicity, surgical complications, and short-term mortality in a randomized trial of neoadjuvant cisplatin/5FU versus epirubicin/cisplatin and capecitabine prior to resection of lower esophageal/gastroesophageal junction (GOJ) adenocarcinoma (MRC OEO5, ISRCTN01852072, CRUK 02/010) – Cunningham D et al

- **Key results**



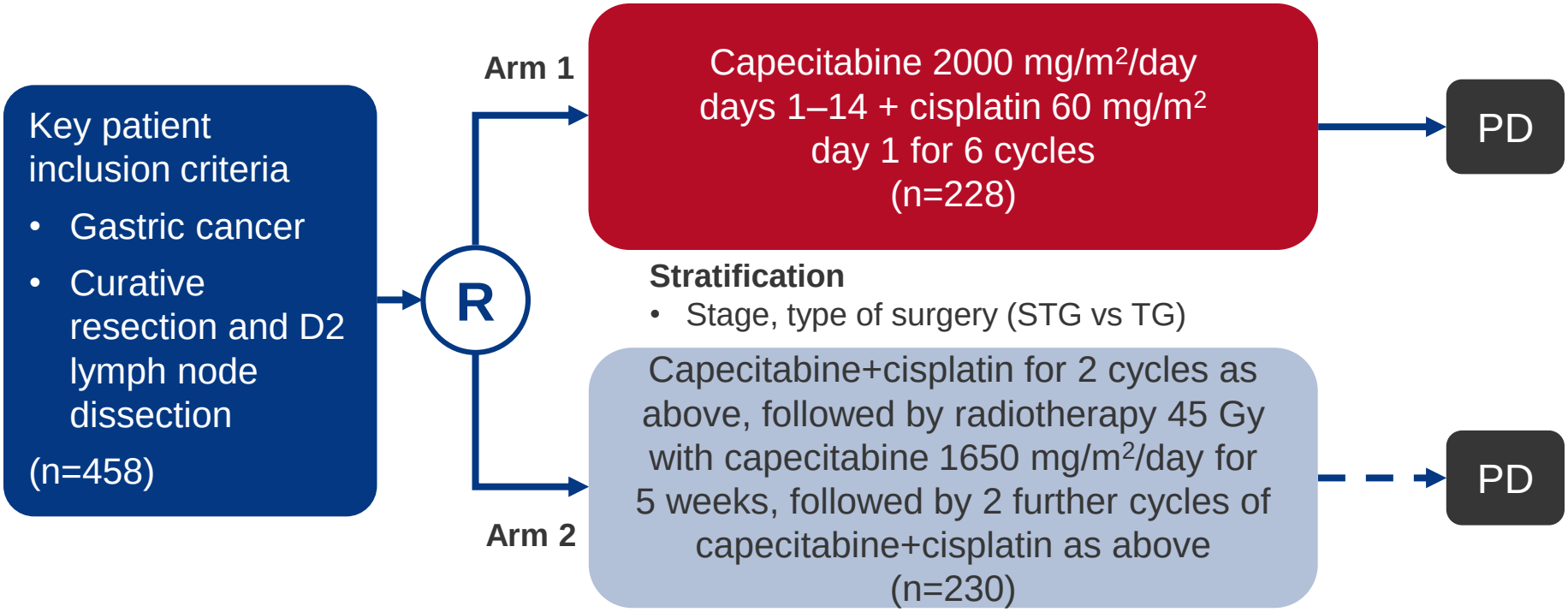


- **Conclusion**
  - **Four cycles of ECX had higher CT-related toxicity vs 2 cycles of CF, but did not affect resection rates, surgical complications or 90-day mortality**

Cunningham et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4014)

4008: Phase III trial to compare capecitabine/cisplatin (XP) versus XP plus concurrent capecitabine-radiotherapy in gastric cancer (GC): The final report on the ARTIST trial – Lee J et al

- **Study objective**
  - To determine whether the addition of RT to capecitabine/cisplatin CT can improve survival in patients with D2 dissected gastric cancer



Primary endpoint

- 3-year DFS

Secondary endpoints

- OS, toxicity profile, exploratory biomarkers

Lee et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4008)

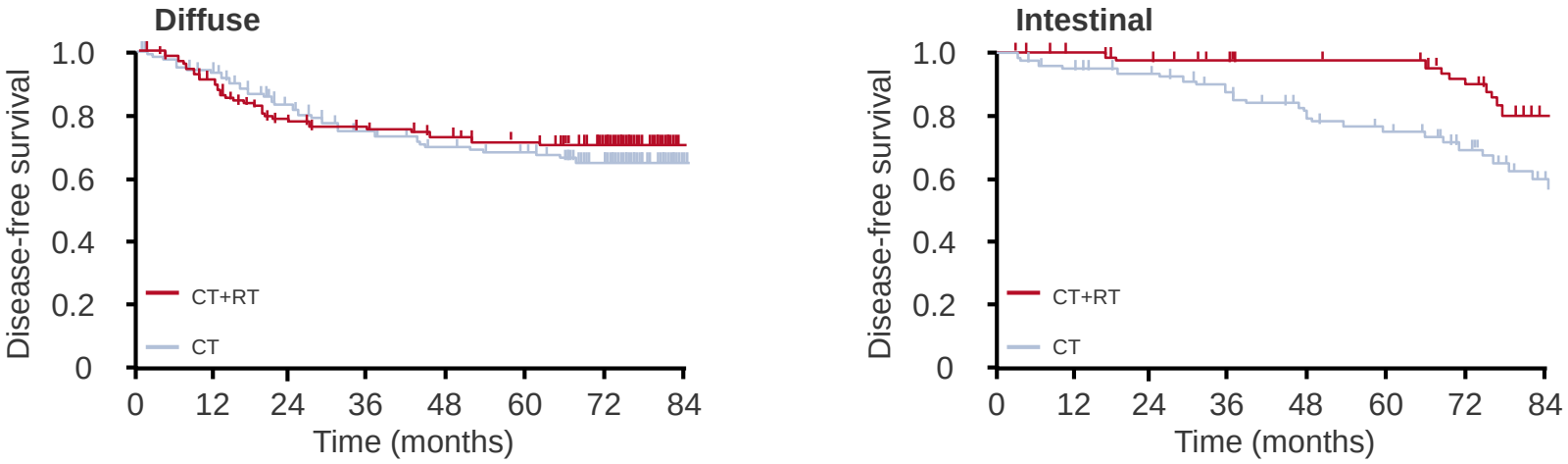
4008: Phase III trial to compare capecitabine/cisplatin (XP) versus XP plus concurrent capecitabine-radiotherapy in gastric cancer (GC): The final report on the ARTIST trial – Lee J et al

- **Key results**

Survival (CT+RT vs CT alone)	HR (95% CI)	p value*
DFS	0.74 (0.52, 1.05)	0.9222
OS	1.13 (95% CI: 0.78, 1.65)	0.5272

  - 3-year DFS for CT+RT vs CT alone:
    - In lymph node-positive disease (n=396) was 76% vs 72% (p=0.04)
    - In intestinal type gastric cancer (n=163) was 94% vs 83% (p=0.001; Figure)

DFS by Lauren classification



Lee et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4008)

4008: Phase III trial to compare capecitabine/cisplatin (XP) versus XP plus concurrent capecitabine-radiotherapy in gastric cancer (GC): The final report on the ARTIST trial – Lee J et al

- **Key results**

Grade 3–4 AEs, n (%)	CT (N=226)		CT+RT (N=227)	
	Grade 3	Grade 4	Grade 3	Grade 4
Nausea	28 (12)	0	28 (12)	0
Vomiting	8 (4)	0	7 (3)	0
Diarrhoea	4 (2)	1 (0)	2 (1)	0
Stomatitis	3 (1)	0	4 (2)	0
Constipation	2 (1)	0	2 (1)	0
Hand-foot syndrome	5 (2)		7 (3)	
Anaemia	3 (1)	1 (0)	1 (0)	0
Neutropenia	79 (35)	13 (6)	99 (44)	11 (5)
Thrombocytopenia	0	0	2 (1)	0

- **Conclusions**
  - **Overall, this trial was negative with no significant difference in DFS with the addition of RT to CT compared with CT alone**
  - **Subgroup analyses showed a potential benefit of RT in patients with intestinal type and lymph node-positive gastric cancer**

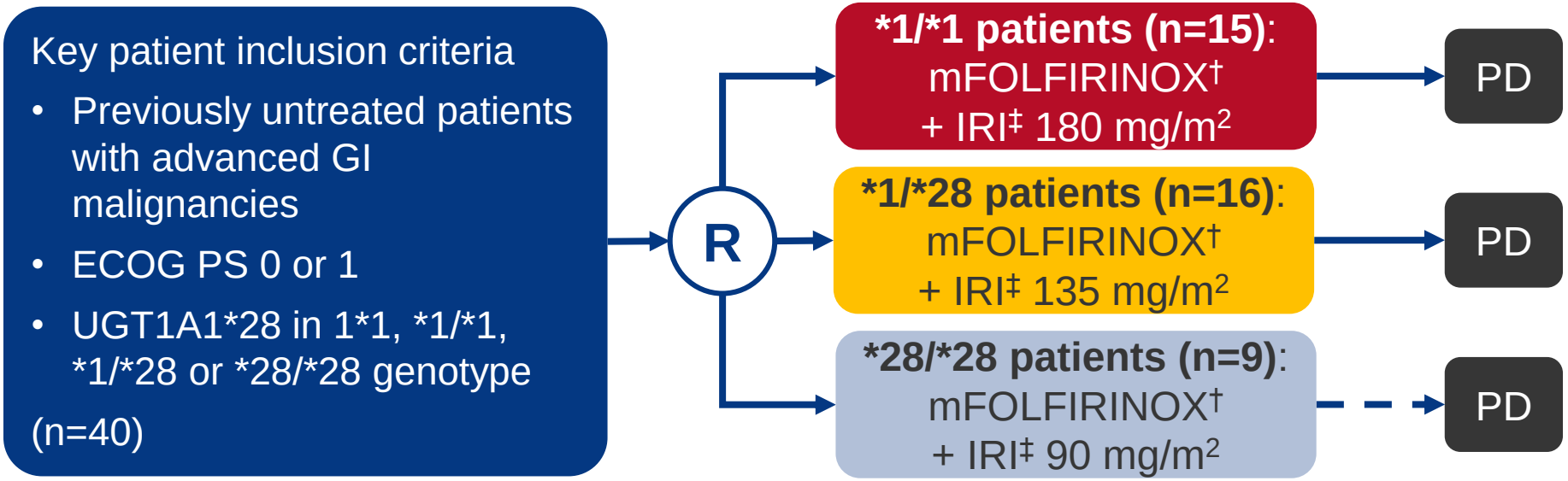
Lee et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4008)

OESOPHAGEAL & GASTRIC CANCER

PALLIATIVE / METASTATIC

4125: A UGT1A1 genotype-guided dosing study of modified FOLFIRINOX (mFOLFIRINOX) in previously untreated patients (pts) with advanced gastrointestinal malignancies – Sharma M et al

- **Study objective**
  - To determine whether genotype-guided dosing of IRI (based on UGT1A1*28 in 1*1, *1/*1, *1/*28 and *28/*28 patients) in mFOLFIRINOX† improves toxicity



Primary endpoint

- DLT

Secondary endpoint

- ORR (RECIST 1.1)

†Every 14 days; ‡5-FU dose 2400 mg/m^2 over 46 h (no bolus); leucovorin 400 mg/m^2; oxaliplatin 85 mg/m^2
DLT, dose-limiting toxicity; IRI, irinotecan

Sharma et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4125)

4125: A UGT1A1 genotype-guided dosing study of modified FOLFIRINOX (mFOLFIRINOX) in previously untreated patients (pts) with advanced gastrointestinal malignancies –Sharma M et al

- **Key results**

UGTIA1 genotype	IRI dose	N	DLT, n (%)	DLT description
*1/*1	180 mg/m^2	15	2 (13)	Neutropenic fever x 2
*1/*28	135 mg/m^2	16	2 (13)	Grade 3 fatigue, diarrhoea, grade 3 fatigue
*28/*28	90 mg/m^2	9	3 (33)	Neutropenic fever x 2, grade 3 abdominal pain

Best response	Pancreatic cancer (N=19)	Biliary tract cancer (N=13)	Gastric cancer (N=6)
PR	11 (58%)	4 (31%)	3 (50%)
SD	6 (32%)	5 (38%)	3 (50%)
PD	2 (10%)	4 (31%)	0

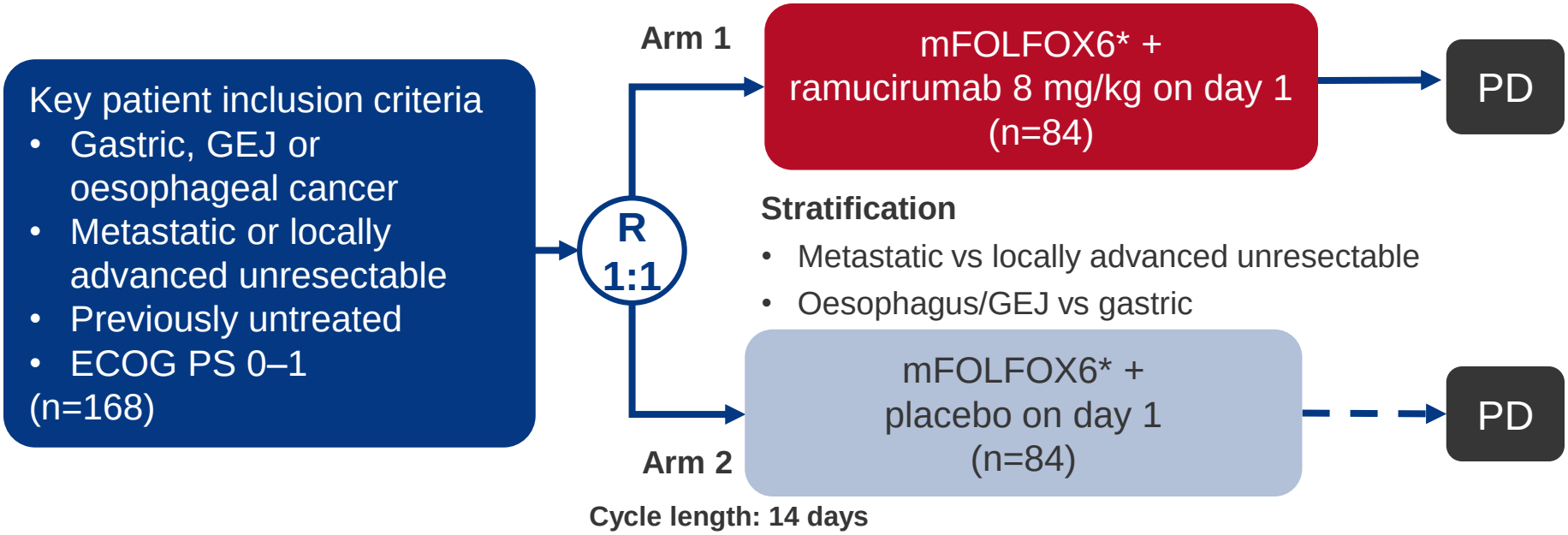
- **Conclusions**
  - **mFOLFIRINOX is tolerable in UGT1A1*1/*1 patients at the standard IRI dose of 180 mg/m^2 and in *1/*28 patients at a reduced IRI dose of 135 mg/m^2**
  - **mFOLFIRINOX is not tolerable in UGT1A1 *28/*28 patients, even at a reduced IRI dose of 90 mg/m^2**

DLT, dose-limiting toxicity

Sharma et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4125)

4004: Ramucirumab (RAM) plus FOLFOX as front-line therapy (Rx) for advanced gastric or esophageal adenocarcinoma (GE-AC): Randomized, double-blind, multicenter phase 2 trial – Yoon HJ et al

- **Study objective**
  - To investigate the addition of ramucirumab to FOLFOX as first-line therapy in patients with gastric or oesophageal adenocarcinoma



Primary endpoint

- PFS

Secondary endpoints

- ORR, OS, time to progression and safety/toxicity

*5-FU 400 mg/m^2 bolus, leucovorin 400 mg/m^2, oxaliplatin 85 mg/m^2, then 5-FU infusion 2400 mg/m^2 (46–48 h)
GEJ, gastro-oesophageal junction

Yoon et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4004)

4004: Ramucirumab (RAM) plus FOLFOX as front-line therapy (Rx) for advanced gastric or esophageal adenocarcinoma (GE-AC): Randomized, double-blind, multicenter phase 2 trial – Yoon HJ et al

- **Key results**

Survival	mFOLFOX6+ ramucirumab (N=84)	mFOLFOX6+ placebo (N=84)	HR (95% CI)	p-value
Median PFS, months				
Overall (ITT population)	6.44	6.74	0.98 (0.69, 1.37)	0.98
Oesophageal	5.8	5.8	1.10 (0.61, 1.97)	0.746
Gastric/GEJ	9.3	7.6	0.53 (0.29, 0.97)	0.036
OS, months				
Overall (ITT population)	11.7	11.5	1.08 (0.73, 1.58)	-
Oesophageal	10.5	11.5	1.29 (0.75, 2.19)	-
Gastric/GEJ	14.6	12.5	0.94 (0.55, 1.61)	-

Best overall tumour response	mFOLFOX6+ramucirumab (N=84)		mFOLFOX6+placebo (N=84)		p-value
	N	%	N	%	
Complete response	6	7	5	6	-
Partial response	32	38	34	40	-
Stable disease	33	39	17	20	-
Progressive disease	6	7	18	21	-
Disease control rate	71	85	56	67	0.008

Yoon et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4004)

4004: Ramucirumab (RAM) plus FOLFOX as front-line therapy (Rx) for advanced gastric or esophageal adenocarcinoma (GE-AC): Randomized, double-blind, multicenter phase 2 trial – Yoon HJ et al

- **Key results**
  - Non-PD treatment discontinuation: RAM 48% vs placebo 16%; difference 32%

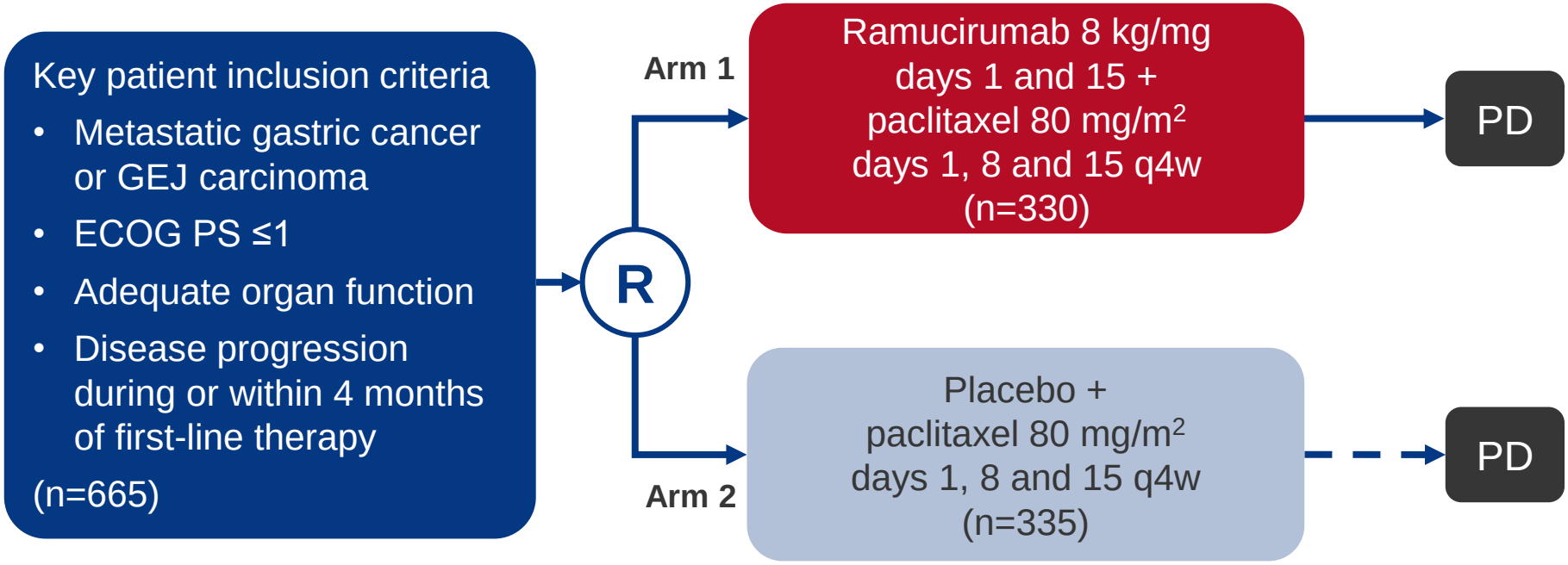
Most common AEs, %		mFOLFOX6+ramucirumab (N=82)		mFOLFOX6+placebo (N=80)	
		Any	≥Grade 3	Any	≥Grade 3
Haematological	Thrombocytopenia	56	6	39	3
Nervous system	Peripheral sensory neuropathy	54	6	53	9
	Headache	23	2	15	0
Metabolism and nutrition	Decreased appetite	42	6	28	0
	Dehydration	28	9	15	1
	Hypokalaemia	20	6	9	3

- **Conclusions**
  - **The addition of ramucirumab to mFOLFOX6 did not improve PFS**
  - **Ramucirumab was associated with a higher disease control rate**
  - **A higher non-progressive disease discontinuation rate and lower drug exposure in ramucirumab arm may have impacted PFS assessment**
  - **Longer PFS was observed with ramucirumab in the gastric/GEJ subgroup**

Yoon et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4004)

4005: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab (RAM) plus paclitaxel (PTX) versus placebo (PL) plus PTX in the treatment of metastatic gastroesophageal junction and gastric adenocarcinoma (mGC) following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy—Efficacy analysis in Japanese and Western patients – Hironaka S et al

- **Study objective**
  - To analyse survival outcomes in Japanese versus Western patients with metastatic gastric cancer or GEJ carcinoma receiving ramucirumab in combination with paclitaxel compared with paclitaxel alone



Primary endpoints

- OS and PFS

Secondary endpoint

- ORR

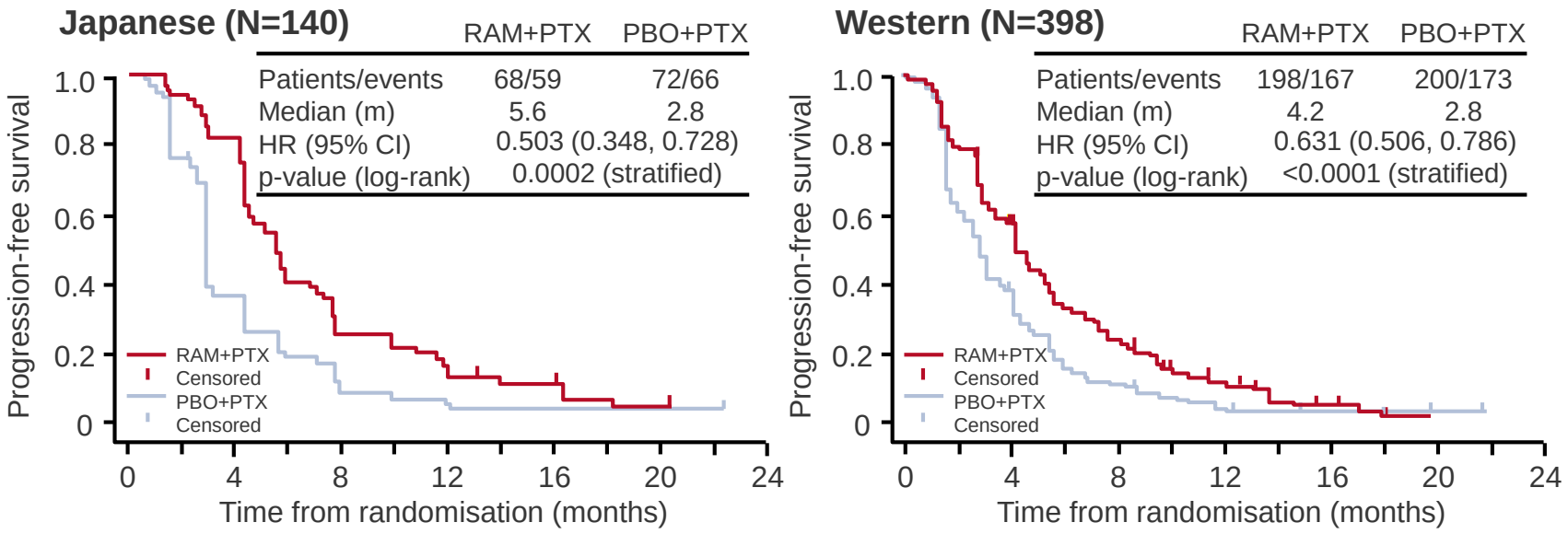
GEJ, gastro-oesophageal junction

Hironaka et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4005)

4005: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab (RAM) plus paclitaxel (PTX) versus placebo (PL) plus PTX in the treatment of metastatic gastroesophageal junction and gastric adenocarcinoma (mGC) following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy—Efficacy analysis in Japanese and Western patients – Hironaka S et al

- **Key results**

PFS



	Japanese		Western	
	Ramucirumab+paclitaxel (n=68)	Placebo+paclitaxel (n=72)	Ramucirumab+paclitaxel (n=198)	Placebo+paclitaxel (n=200)
Median OS, months	11.4	11.5	8.6	5.9
HR (95% CI)	0.88o (0.603, 1.284)		0.726 (0.580, 0.909)	
p-value	0.5113		0.0050	

Hironaka et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4005)

4005: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab (RAM) plus paclitaxel (PTX) versus placebo (PL) plus PTX in the treatment of metastatic gastroesophageal junction and gastric adenocarcinoma (mGC) following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy—Efficacy analysis in Japanese and Western patients – Hironaka S et al

- **Key results**
  - PDT: Japan 75.0 vs 75.0%; West 38.4 vs 36.0% with ramucirumab vs placebo, respectively

Grade 3 AEs occurring in >5% in any group, %	Japanese		Western	
	RAM+PTX (n=68)	PBO+PTX (n=71)	RAM+PTX (n=196)	PBO+PTX (n=197)
Neutropenia	66.2	25.4	32.1	14.7
Leukopenia	45.6	14.1	9.7	4.1
Neuropathy	4.4	5.6	11.2	5.6
Decreased appetite	2.9	5.6	2.6	2.5
Fatigue	1.5	2.8	16.8	6.6
Hypertension	4.4	0	18.9	2.5
Abdominal pain	0	0	7.1	4.6

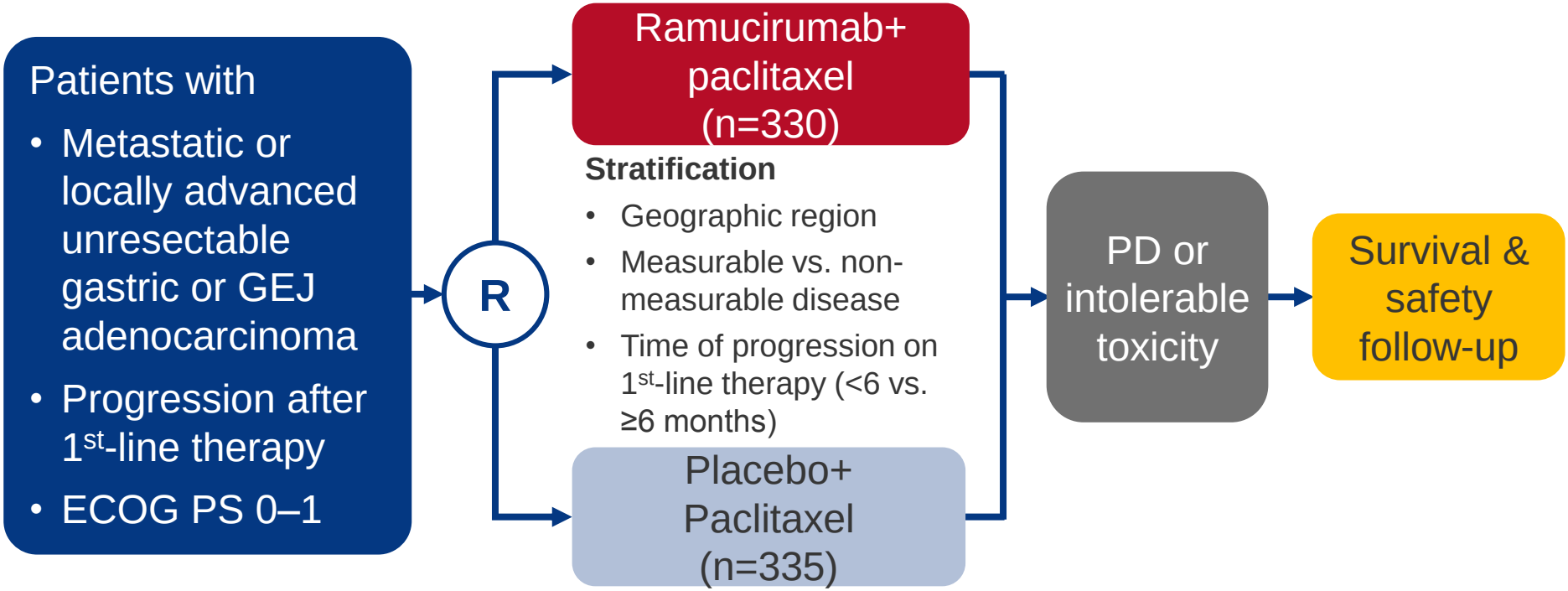
- **Conclusions**
  - **There were improvements in PFS and ORR in the Japanese population, which was consistent with the Western population**
  - **Prolonged post-progression survival in Japanese patients may be due to higher use of PDT and may have masked the potential OS benefit**
  - **The safety profile was generally comparable between Japanese and Western patients, although some AEs were more frequent in Japanese patients**

PDT, post-discontinuation treatment

Hironaka et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4005)

LBA7: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy RAINBOW IMCL CP12-0922 (I4T-IE-JVBE) – Wilke H et al

- **Study objective**
  - To assess the efficacy of second-line treatment with ramucirumab in combination with paclitaxel compared with paclitaxel alone in patients with gastric cancer



Primary endpoint

- OS

Secondary endpoints

- PFS, TTP, ORR, safety, QoL, PK, PD

Ramucirumab 8 mg/kg days 1 & 15;
Paclitaxel 80 mg/m^2 days 1, 8 & 15 of 28-day cycle

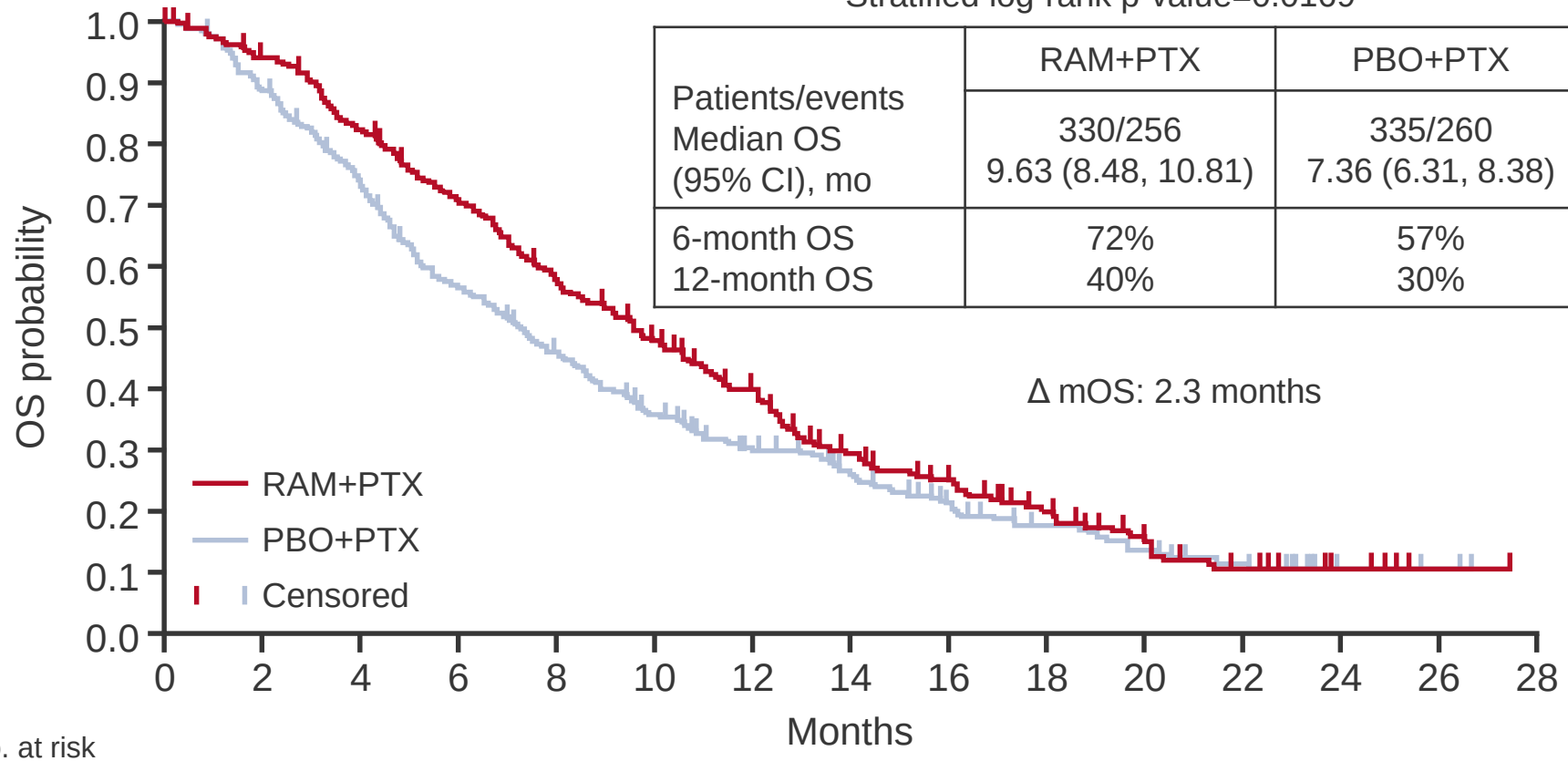
Wilke et al. J Clin Oncol 2014; 32 (suppl 3; abstr LBA7)

LBA7: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy RAINBOW IMCL CP12-0922 (I4T-IE-JVBE) – Wilke H et al

- **Key results**

HR 0.807 (95% CI 0.678, 0.962)
Stratified log-rank p-value=0.0169

	RAM+PTX	PBO+PTX
Patients/events Median OS (95% CI), mo	330/256 9.63 (8.48, 10.81)	335/260 7.36 (6.31, 8.38)
6-month OS 12-month OS	72% 40%	57% 30%



No. at risk

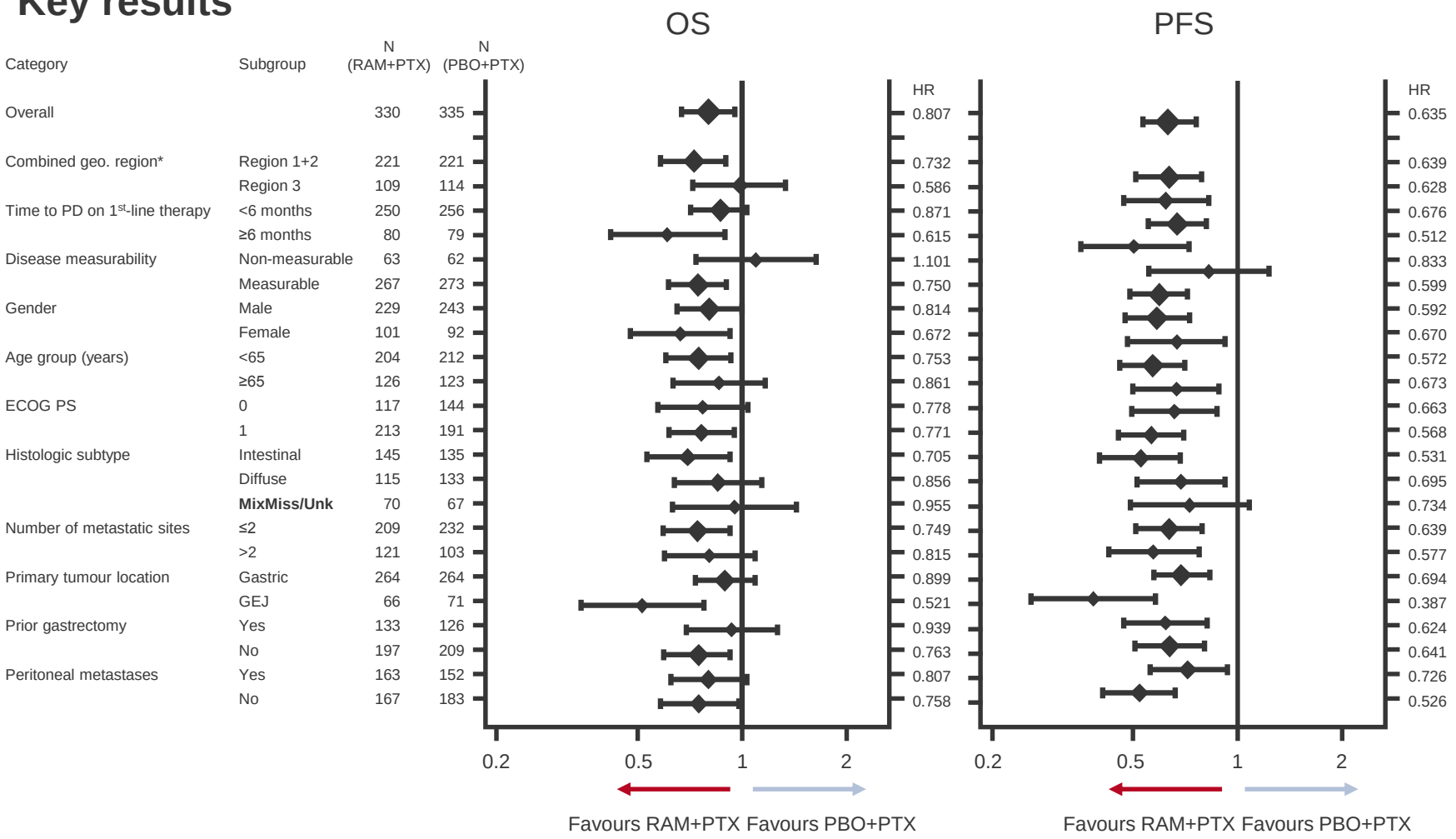
RAM+PTX	330	308	267	228	185	148	116	78	60	41	24	13	6	1	0
PBO+PTX	335	294	241	180	143	109	81	64	47	30	22	13	5	2	0

PTX, paclitaxel; RAM, ramucirumab

Wilke et al. J Clin Oncol 2014; 32 (suppl 3; abstr LBA7)

LBA7: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy RAINBOW IMCL CP12-0922 (I4T-IE-JVBE) – Wilke H et al

- **Key results**



*Region 1: Europe. United States and Australia. Region 2: Brazil, Chile, Mexico and Argentina. Region 3: Japan, South Korea, Hong, Taiwan and Singapore

Wilke et al. J Clin Oncol 2014; 32 (suppl 3; abstr LBA7)

LBA7: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy RAINBOW IMCL CP12-0922 (I4T-IE-JVBE) – Wilke H et al

- **Key results**
  - Ramucirumab in combination with paclitaxel provided a consistent additive effect across all efficacy endpoints

Efficacy parameter	Ramucirumab +paclitaxel	Placebo+ paclitaxel	HR p-value	Delta
Response rate, %	28	16	=0.0001	+12
Disease control rate, %	80	64	<0.0001	+16
Median PFS, months At 6 months, % At 9 months, %	4.40 36 22	2.86 17 10	HR 0.635 <0.0001	+1.5 +19 +12
Median OS, months At 6 months, % At 12 months, %	9.63 72 40	7.36 57 30	HR 0.807 =0.0169	+2.3 +15 +10

  - Grade ≥3 TEAEs that occurred in >10% of patients and at a higher incidence with ramucirumab+paclitaxel were: neutropenia, leukopenia, hypertension and fatigue; febrile neutropenia was low and similar between the two treatment groups

Wilke et al. J Clin Oncol 2014; 32 (suppl 3; abstr LBA7)

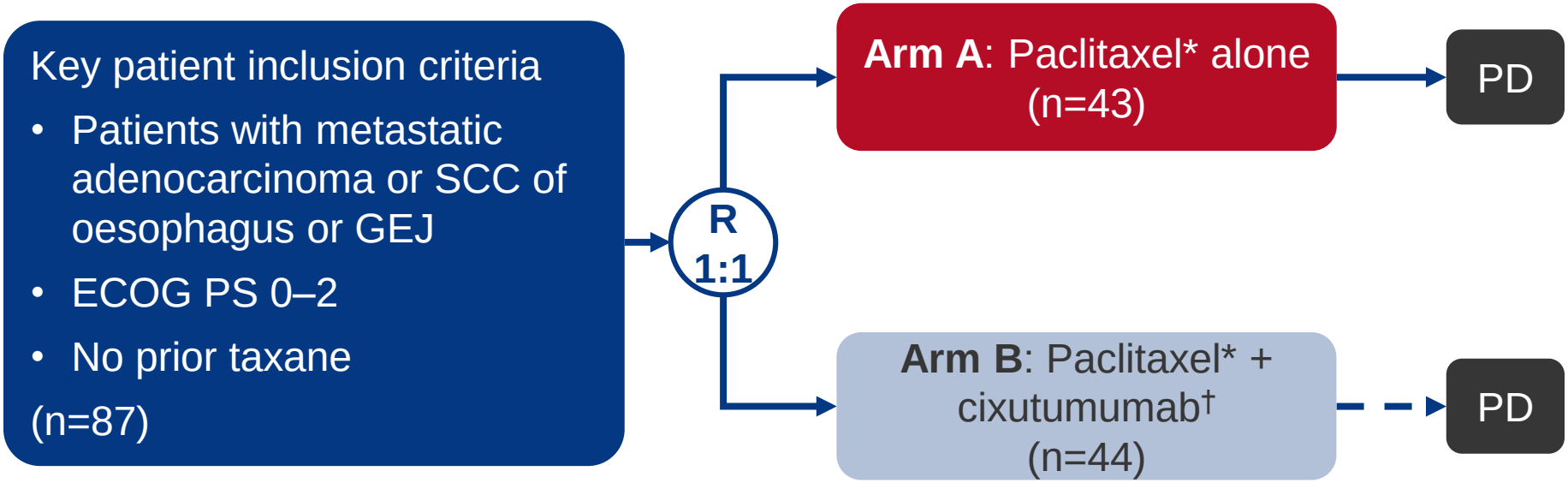
LBA7: RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy RAINBOW IMCL CP12-0922 (I4T-IE-JVBE) – Wilke H et al

- **Conclusions**
  - **Ramucirumab in combination with paclitaxel provided a significant and clinically meaningful OS benefit of >2 months; risk reduction of death by 19%**
  - **Significant benefits were also observed for PFS and ORR**
  - **Ramucirumab is an effective new drug for the treatment of patients with metastatic or locally advanced unresectable gastric or GEJ cancer who have received prior chemotherapy**
  - **The findings demonstrate that second-line therapy improves survival of patients with metastatic or locally advanced unresectable gastric cancer**

Wilke et al. J Clin Oncol 2014; 32 (suppl 3; abstr LBA7)

4020: E2208: Randomized phase II study of paclitaxel with or without the anti-IGF-IR antibody cixutumumab (IMC-A12) as second-line treatment for patients with metastatic esophageal or GE junction cancer – Cohen SJ et al

- **Study objective**
  - To compare paclitaxel alone with paclitaxel+cixutumumab in patients as second-line treatment for patients with metastatic oesophageal or gastro-oesophageal junction (GEJ) cancer



Primary endpoint

- PFS

Secondary endpoints

- OS, RR and toxicity

*80 mg/m^2 IV days 1,8,15 q4w; †10 mg/kg days 1,15 q4w

Cohen et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4020)

4020: E2208: Randomized phase II study of paclitaxel with or without the anti-IGF-IR antibody cixutumumab (IMC-A12) as second-line treatment for patients with metastatic esophageal or GE junction cancer – Cohen SJ et al

- **Key results**

Most common AEs, n (%)	Arm A (Grade 3)	Arm A (Grade 4)	Arm B (Grade 3)	Arm B (Grade 4)
Anaemia	4 (10)	0	3 (7)	1 (2)
Fatigue	3 (8)	0	1 (2)	0
Generalised muscle weakness	0	0	2(5)	0
Hyperglycaemia	2 (5)	0	5 (11)	0
Hypophosphataemia	2 (5)	0	1 (2)	0
Lymphopenia	7 (18)	1 (3)	7 (16)	1 (2)
Mucositis	0	0	2 (5)	0
Neutropenia	3 (8)	0	5 (11)	3 (7)
Vomiting	0	0	2 (5)	0

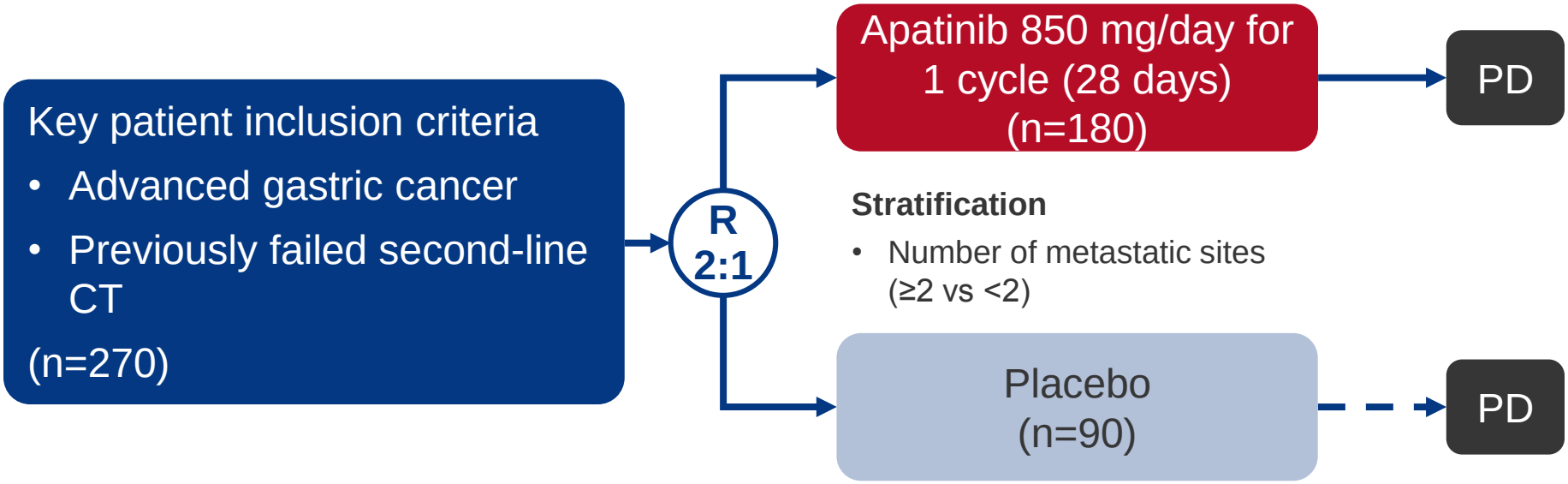
  - Median PFS: paclitaxel 2.6 m vs paclitaxel+cixutumumab 2.3 m (p=0.72)
  - Median OS: paclitaxel 6.5 m vs paclitaxel+cixutumumab 6.4 (p=0.92)
  - RR (CR+PR): 12% with paclitaxel vs 14% with paclitaxel+cixutumumab

- **Conclusion**
  - **The addition of cixutumumab to paclitaxel in second-line therapy was well tolerated, but did not improve clinical outcome**

Cohen et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4020)

4003: Phase III study of apatinib in advanced gastric cancer: A randomized, double-blind, placebo-controlled trial – Qin S et al

- **Study objective**
  - To assess the efficacy and safety of apatinib (a VEGFR-2 tyrosine kinase inhibitor) in patients with advanced gastric cancer who have previously failed second-line CT



Primary endpoint

- OS

Qin et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4003)

4003: Phase III study of apatinib in advanced gastric cancer: A randomized, double-blind, placebo-controlled trial – Qin S et al

- **Key results**

	Apatinib	Placebo	HR (95% CI)	p-value
Median OS, days	195	140	0.71 (0.54, 0.94)	<0.016
Median PFS, days	78	53	0.44 (0.33, 0.61)	<0.0001
ORR, %	2.8	0		

  - Apatinib was generally well tolerated
    - Most AEs were managed by dose interruptions or reductions
    - Grade 3–4 AEs that occurred in >2% of patients were: hypertension, hand-and-foot syndrome, proteinuria, fatigue, anorexia and elevated aminotransferase

- **Conclusions**
  - **This study provides further evidence of the efficacy and safety of apatinib in the patients with advanced gastric cancer**
  - **The recommended dose of apatinib for clinical use is 850 mg/day**

Qin et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4003)

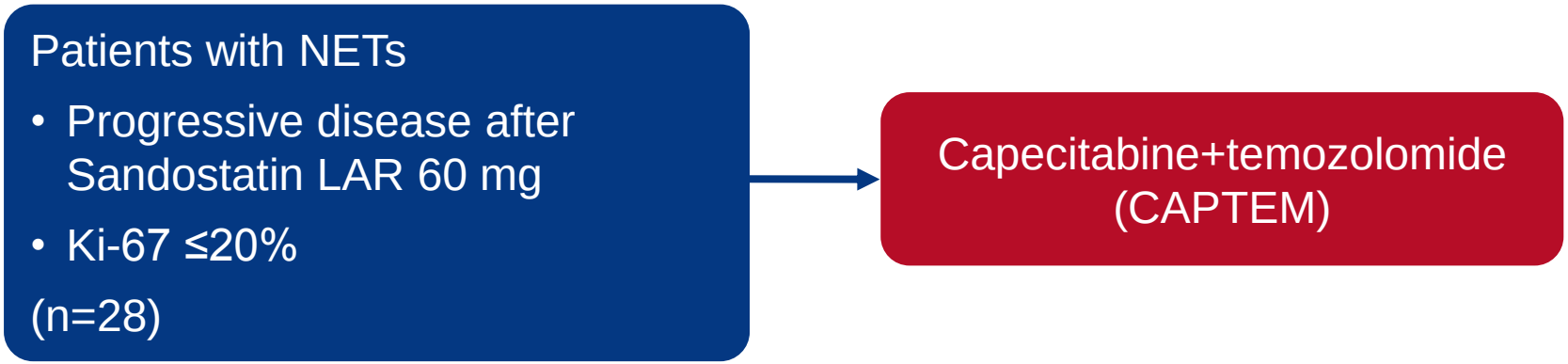
RARE TUMOURS

RARE TUMOURS

NEUROENDOCRINE TUMOURS

179: Prospective phase II study of capecitabine and temozolomide (CAPTEM) for progressive, moderately, and well-differentiated metastatic neuroendocrine tumors – Fine RL et al

- **Study objective**
  - To assess treatment with capecitabine and temozolomide in patients with progressive, metastatic, well- or moderately-differentiated neuroendocrine tumours (NETs) who failed Sandostatin LAR 60 mg



Primary endpoint

- Response rate (RR)

Secondary endpoints

- PFS, OS, safety

Capecitabine 1500 mg/m^2/day (PO divided BID, max 2500 mg/day) on days 1–14 ; temozolomide 150–200 mg/m^2/day (PO divided bid, lower dose for patients who had prior chemotherapy or extensive radiation) on days 1–14

Suntharalingam et al. J Clin Oncol 2014; 32 (suppl 3; abstr LBA6)

179: Prospective phase II study of capecitabine and temozolomide (CAPTEM) for progressive, moderately, and well-differentiated metastatic neuroendocrine tumors – Fine RL et al

- **Key results**
  - Interim findings showed an overall RR of 43% (CR 11%, PR 32%) and SD rate of 54%, with a clinical benefit in 97%
    - In carcinoid tumours (typical and atypical), the ORR was 41%

	% SD	% PR	% CR	% PD	PFS, mo	OS, mo
Carcinoid (total) (n=12)	58	33	8	0	>23.9	>31.5
Typical (n=10)	60	30	10	0	>23.9	>28.3
Atypical (n=2)	50	50	0	0	>23.8	>27.4
Pituitary (n=3)	0	33	67	0	>41.6	>41.6
Pancreatic NET (n=11)	55	36	0	9	>20.0	>24.4
Medullary thyroid (n=2)	100	0	0	0	>22.8	>27.7
Overall (n=28)	54	32	11	3	>22.2	>29.1

  - Most common grade 3/4 toxicities were lymphopenia (35%), hyperglycaemia (6%, unlikely related), thrombocytopenia (3%) and diarrhoea (3%)

Fine et al. J Clin Oncol 2014; 32 (suppl 3; abstr 179)

179: Prospective phase II study of capecitabine and temozolomide (CAPTEM) for progressive, moderately, and well-differentiated metastatic neuroendocrine tumors – Fine RL et al

- **Conclusions**
  - CAPTEM was associated with significant response rates (RR 43%, SD 54%) in patients with various types of NET
    - PFS and OS analysis is ongoing
  - Significant responses were also observed in the traditionally chemo-resistant carcinoids (RR 42%, SD 58%) and pituitary tumours (RR 100%, CR 2/3)

Fine et al. J Clin Oncol 2014; 32 (suppl 3; abstr 179)

RARE TUMOURS

PSEUDOMYXOMA PERITONEI

4033: Nomograms to predict prognosis in pseudomyxoma peritonei: A Peritoneal Surface Oncology Group International (PSOGI) multicenter study – Kusamura S et al

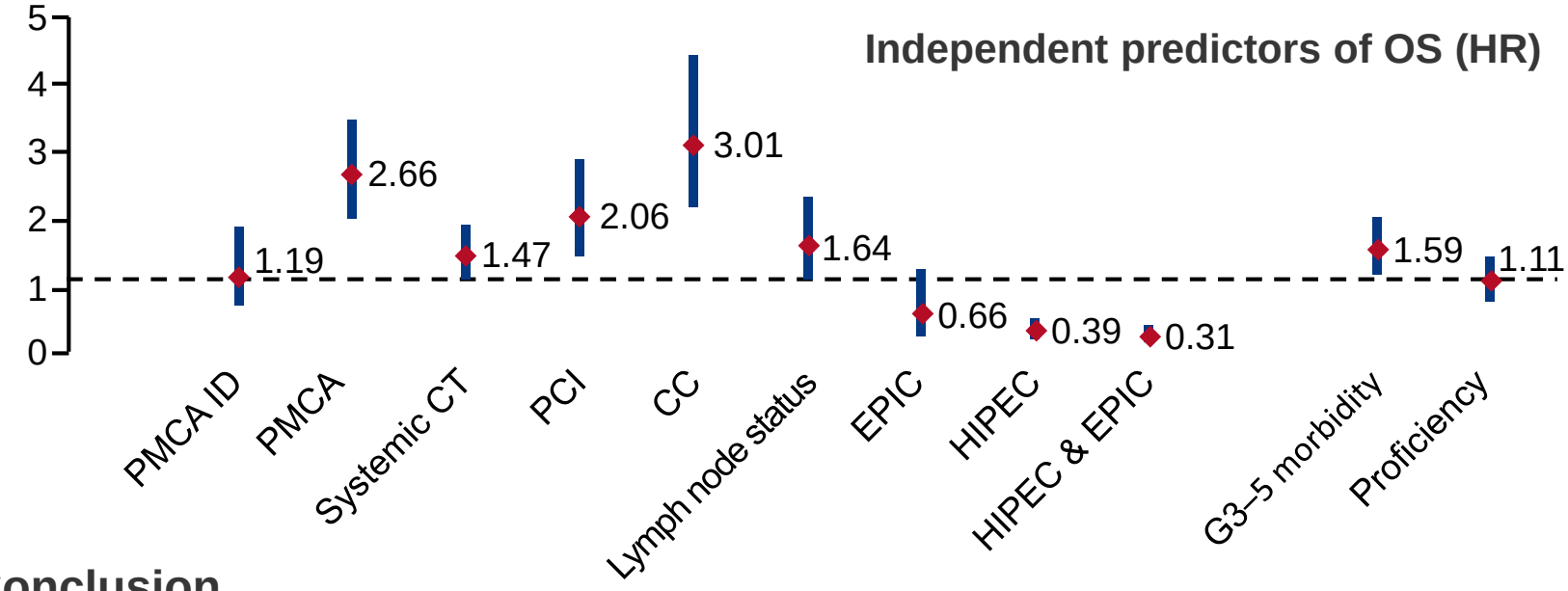
- **Study objective**
  - To determine whether clinico-pathological variables can predict survival in patients with PMP treated with cytoreductive surgery and intraperitoneal CT
- **Study design**
  - The developing set comprised data from 1715 PMP patients from 29 centres
  - The covariates were chosen according to literature data
  - Continuous variables were transformed using restricted cubic splines
  - Missing data were handled using multiple imputation with chained equations (MICE) approach
  - A Cox model was fitted in each of the different completed developing datasets generated by MICE
  - Pooled estimates of regression coefficients, variances, and models' discriminations (bootstrap corrected Harrell C indexes) were obtained using Rubin's rule
  - The nomograms were externally validated on 733 PMP patients (validating set)

PMP, pseudomyxoma peritonei

Kusamura et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4033)

4033: Nomograms to predict prognosis in pseudomyxoma peritonei: A Peritoneal Surface Oncology Group International (PSOGI) multicenter study – Kusamura S et al

- **Key results**
  - 5-year OS: 74.1% (95% CI 71.3, 76.8); 5-year PFS: 52.3% (95% CI 49.4, 55.2)
  - Adjusted OS/PFS were 0.80/0.74 (developing set), 0.74/0.72 (validating set)



- **Conclusion**
  - **The nomograms may allow the prediction of OS and PFS, providing individualised outcome prognostication**

*Corrected Harrell C indexes; CC, completeness of cytoreduction; EPIC, early postoperative CT; HIPEC, hyperthermic intraperitoneal CT; PCI, peritoneal cancer index

Kusamura et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4033)