# GI SLIDE DECK 2014

## Selected abstracts from:

## ESMO 2014 Congress

26–30 Sept 2014 | Madrid, Spain

esdo
european society of digestive oncology

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# Letter from ESDO

Dear Colleagues

It is my pleasure to present this ESDO slide set which has been designed to highlight and summarise key findings in digestive cancers from the major congresses in 2014. This slide set specifically focuses on the European Society for Medical Oncology Congress.

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

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

Yours sincerely,

Eric Van Cutsem
Phillippe Rougier
Thomas Seufferlein
(ESDO Governing Board Executives)

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european society of digestive oncology

# ESDO Medical Oncology Slide Deck Editors 2014



## Colorectal cancers

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## Biomarkers

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esdo

# Glossary

| | |
|---|---|
| 5-FU | 5-fluorouracil |
| AE | adverse event |
| AFP | alpha-fetoprotein |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BCLC | Barcelona Clinic Liver Cancer |
| BSC | best supportive care |
| CBR | clinical benefits rate |
| CI | confidence interval |
| CR | complete response |
| CRC | colorectal cancer |
| CUP | carcinoma of unknown primary |
| DCR | disease control rate |
| DFS | disease-free survival |
| dMMR | deficient mismatch repair |
| DoR | duration of response |
| ECOG | Eastern Cooperative Oncology Group |
| EGFR | epidermal growth factor receptor |
| FFPE | formalin-fixed, paraffin-embedded |
| FOLFIRI | leucovorin/5-FU/irinotecan |
| FOLFIRINOX | leucovorin/5-FU/irinotecan/oxaliplatin |
| FOLFOX | leucovorin/5-FU/oxaliplatin |
| GEC | gastroesophageal cancer |
| GEJ | gastroesophageal junction |
| GEP | gastroenteropancreatic |
| GI | gastrointestinal |
| GGT | gamma-glutamyl transferase |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| ITT | intention-to-treat |
| LCNEC | large cell neuroendocrine carcinoma |
| LDH | lactate dehydrogenase |
| mAB | monoclonal antibodies |
| mCRC | metastatic CRC |
| MSI | microsatellite instability |
| MSS | microsatellite stable |
| Mut | mutant |
| NET | neuroendocrine tumour |
| NR | not reached |
| ORR | overall response rate |
| OS | overall survival |
| PD | progressive disease |
| pERK | phosphorylated extracellular signal-regulated kinase |
| pMMR | proficient mismatch repair |
| pNET | pancreatic NET |
| PFS | progression free survival |
| PPI | proton pump inhibitor |
| PR | partial response |
| PS | performance status |
| RR | response rate |
| SD | stable disease |
| SoC | standard of care |
| TTF | time to treatment failure |
| TTP | time to progression |
| QoL | quality of life |
| VEGF | vascular endothelial growth factor |
| VEGFR | VEGF receptor |
| WHO | World Health Organization |
| wt | wild-type |

# Contents



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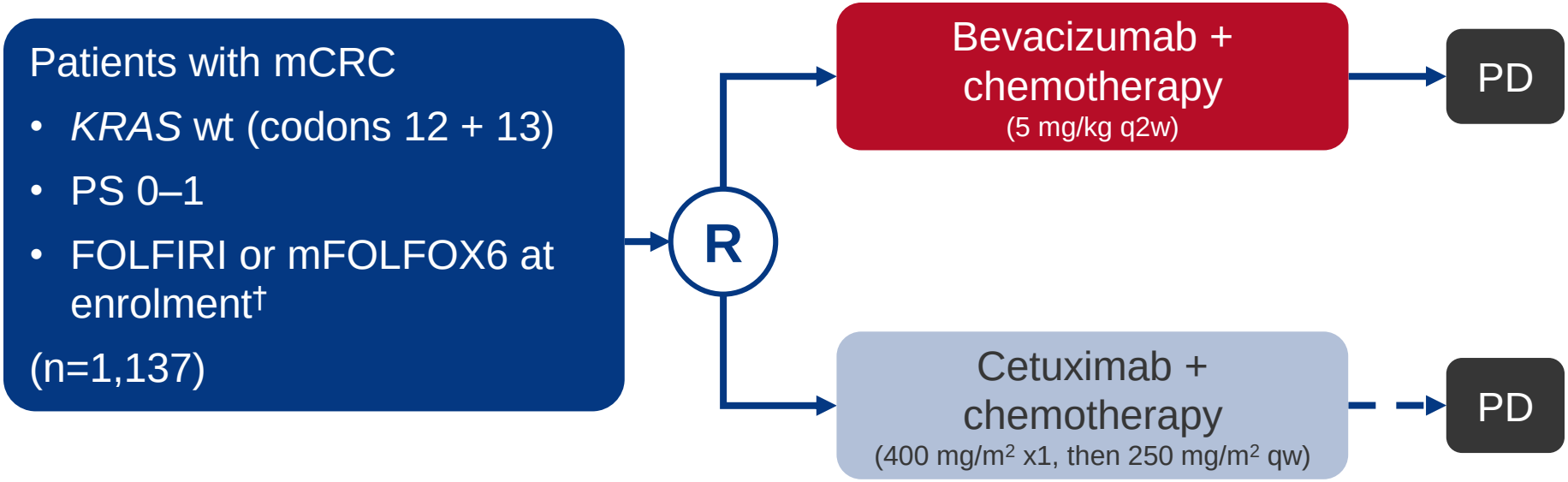
# COLORECTAL CANCER

COLORECTAL CANCER

# NEOADJUVANT THERAPY

## LBA10: CALGB/SWOG 80405: Analysis of patients undergoing surgery as part of treatment strategy – Venook A et al.

- **Study objective**
  - Secondary analysis to determine the long-term outcomes of patients with mCRC who were enrolled in the CALGB/SWOG trial* and underwent surgery after chemotherapy




**180 patients underwent surgery after chemotherapy and were included in the current analysis: bevacizumab + chemotherapy (n=75) vs. cetuximab + chemotherapy (n=105)**

*Phase III first-line treatment study in unselected patients;
†physician/patient choice

Venook et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA10

## LBA10: CALGB/SWOG 80405: Analysis of patients undergoing surgery as part of treatment strategy – Venook A et al.

- **Key results**
  - 132/180 *KRAS* wt patients had no evidence of disease post surgery

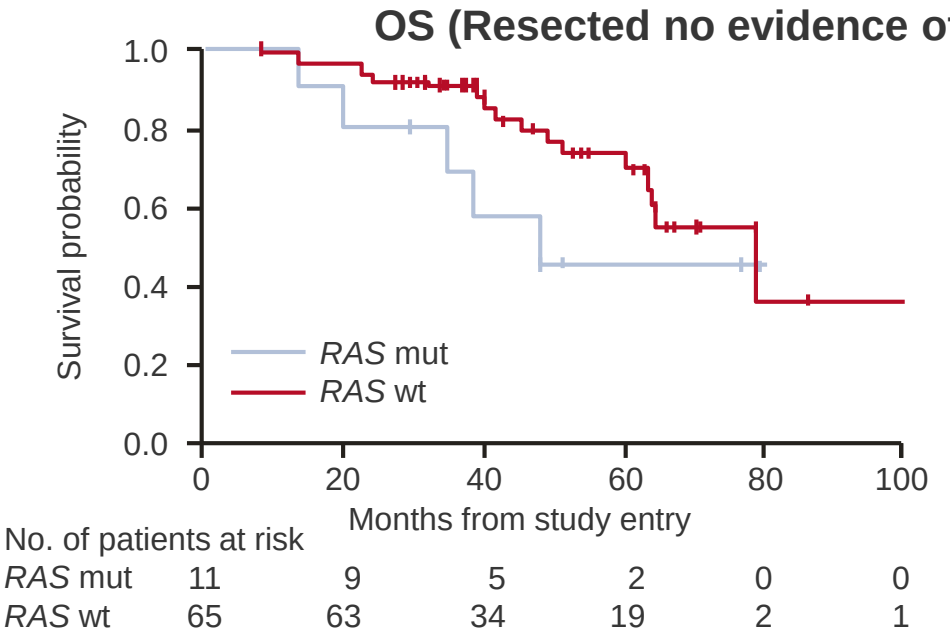
| Resected no evidence of disease | Bevacizumab + chemotherapy (N=50) | Cetuximab + chemotherapy (N=82) | HR (95% CI) | p-value |
|---|---|---|---|---|
| Median OS, months | 67.4 | 64.1 | 1.2 (0.6, 2.2) | 0.56 |
| Median post-surgical recurrence, months | 24.8 | 25.9 | 1.0 (0.6, 1.5) | 0.84 |
| Median DFS, months | 16.9 | 15.3 | 1.0 (0.6, 1.5) | 0.94 |

| Response, % | Bevacizumab + chemotherapy | Cetuximab + chemotherapy |
|---|---|---|
| Overall (N=733) | | |
| ORR | 57 | 66 |
| Resected, no evidence of disease | 45 | 66 |
| CR, PR | 37 (82%) | 50 (76%) |
| No response | 8 | 16 |

Venook et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA10

# LBA10: CALGB/SWOG 80405: Analysis of patients undergoing surgery as part of treatment strategy – Venook A et al.

- **Key results (cont.)**




| *RAS* status | N (events) | Median (95% CI) | HR (95% CI) | p-value |
|---|---|---|---|---|
| wt | 65 (17) | 78.8 (63, NR) | 0.52 (0.2, 1.4) | 0.2 |
| mut | 11 (5) | 47.9 (13.4, NR) | | |

- **Conclusions**
  - **Patients receiving cetuximab + chemotherapy were more likely to undergo curative surgery than those on bevacizumab + chemotherapy**
  - **Outcomes were similar between treatment groups**
  - **Expanded *RAS* may distinguish prognosis**

Venook et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA10

# 505PD: Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine +/- oxaliplatin in locally advanced rectal cancer: Interim analysis for disease-free survival of PETACC 6 – Schmoll H et al.

- **Study objective**
  - To determine whether oxaliplatin plus preoperative chemoradiotherapy and adjuvant chemotherapy improves DFS in locally advanced rectal cancer
- **Study design**
  - Patients with T3/4 ± N+ rectal cancer ≤12 cm from anal verge (ECOG PS 0–2) were randomised to pre- and post-operative capecitabine* ± oxaliplatin†
- **Key results**
  - Total events for DFS: 124 capecitabine vs. 121 capecitabine + oxaliplatin

| 3-year outcomes | Capecitabine (N=547) | Capecitabine + oxaliplatin (N=547) | HR | p-value |
|---|---|---|---|---|
| DFS‡ | 74.5% | 73.9% | 1.04 | 0.78 |
| Loco-regional relapse | 7.6% | 4.6% | - | 0.094 |
| Distant relapse | 19.2% | 17.6% | - | 0.542 |

- **Conclusion**
  - **The addition of oxaliplatin to capecitabine reduced compliance and did not appear to improve efficacy compared with capecitabine alone**

*Pre-operative 825 mg/m² po bid plus chemoradiation, post-operative 1000 m² po bid for 6 cycles; †pre-operative 50 mg/m² iv, post-operative 130 mg/m² iv for 6 cycles; ‡Primary endpoint

Schmoll et al. Ann Oncol 2014; 25 (suppl 4): abstr 505PD

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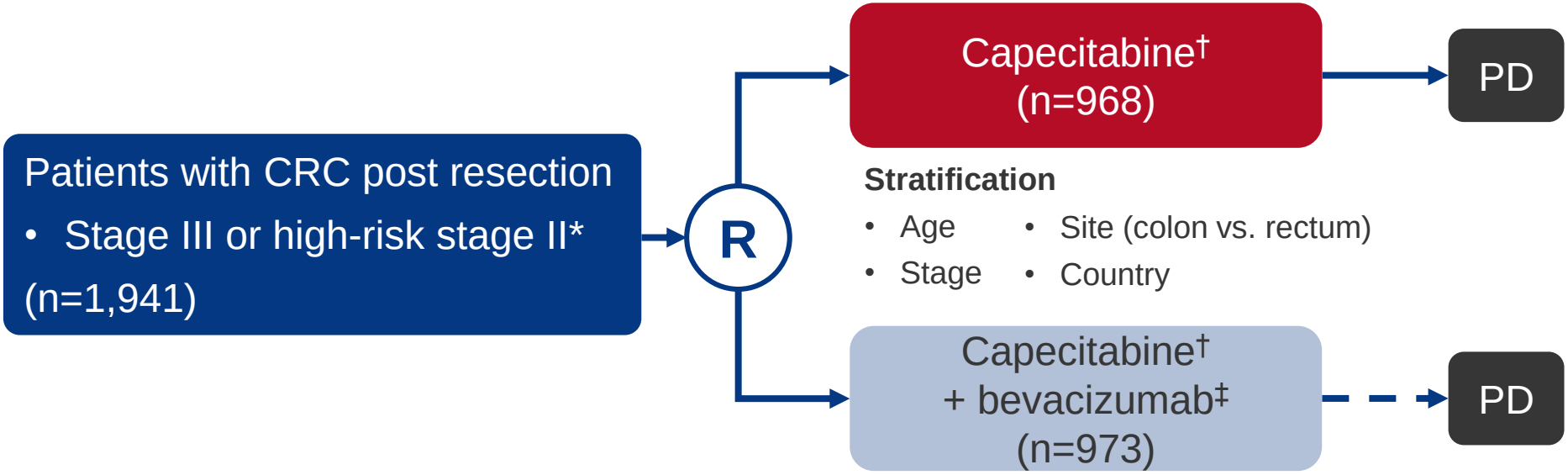
# ADJUVANT THERAPY

# LBA12: Final results from QUASAR2, a multicentre, international randomised phase III trial of capecitabine (CAP) +/- bevacizumab (BEV) in the adjuvant setting of stage II/III colorectal cancer (CRC) – Midgley R et al.

- **Study objective**
  - To assess whether bevacizumab added to capecitabine improves survival in patients with CRC after R0 resection




**Primary endpoint**

- DFS

**Secondary endpoints**

- DFS, OS
- Toxicity, translational science

*T4, Ly1, V1, obstruction, perforation;
†1250 mg/m$^2$ bid d1–14 q3w for 8 cycles (24 weeks);
‡7.5 mg/kg d1: 30–60 min iv infusion q3w for 16 cycles (48 weeks)

Midgley et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA12
Presented by R Kerr

# LBA12: Final results from QUASAR2, a multicentre, international randomised phase III trial of capecitabine (CAP) +/- bevacizumab (BEV) in the adjuvant setting of stage II/III colorectal cancer (CRC) – Midgley R et al.

- **Key results**

| CTCAE | Capecitabine alone, n (%) (N=963) | Capecitabine + bevacizumab, n (%) (N=959) | RR (95% CI) | p-value |
|---|---|---|---|---|
| **Hypertension** | | | All grades | |
| Grade 1/2 | 69 (7.2) | 284 (29.6) | 4.3 (3.4, 5.4) | <0.001 |
| Grade 3/4 | 6 (0.6) | 36 (3.8) | | |
| **Proteinuria** | | | All grades | |
| Grade 1/2 | 48 (5.0) | 188 (19.6) | 4.0 (3.0, 5.4) | <0.001 |
| Grade 3/4 | 1 (0.1) | 9 (0.9) | | |
| **Poor wound healing** | | | All grades | |
| Grade 1/2 | 17 (1.8) | 28 (2.9) | 1.8 (1.0, 3.2) | 0.05 |
| Grade 3/4 | 0 | 2 (0.2) | | |
| **Hand-foot syndrome** | | | Grades 3 and 4 | |
| Grade 1/2 | 555 (57.6) | 526 (54.8) | 1.3 (1.1, 1.5) | 0.002 |
| Grade 3/4 | 201 (20.9) | 257 (26.8) | | |
| **Epistaxis** | | | All grades | |
| All grades | 13 (1.3) | 132 (13.8) | 10.2 (5.8, 17.9) | <0.001 |

  - Possible treatment-related deaths: 0.9% capecitabine vs. 1.9% capecitabine + bevacizumab (RR 2.3; CI 1.0, 5.2); p=0.05
  - 3-year DFS: 78.4% capecitabine vs. 75.4% with capecitabine + bevacizumab (HR 1.06; p=0.5)

Midgley et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA12

# LBA12: Final results from QUASAR2, a multicentre, international randomised phase III trial of capecitabine (CAP) +/- bevacizumab (BEV) in the adjuvant setting of stage II/III colorectal cancer (CRC) – Midgley R et al

- **Key results (cont.)**

| DFS, subgroup analysis | | Capecitabine alone | Capecitabine + bevacizumab | HR* (95% CI) |
|---|---|---|---|---|
| Treatment unadjusted | | 256/968 | 269/973 | 1.06 (0.89, 1.25) |
| Age, years | 60–69 | 101/394 | 108/388 | 1.14 (0.87, 1.49) |
| | 50–59 | 43/197 | 43/192 | 1.01 (0.66, 1.55) |
| | <50 | 24/93 | 22/96 | 0.89 (0.50, 1.59) |
| | 70+ | 88/284 | 96/297 | 1.02 (0.76, 1.36) |
| Disease site | Colon | 226/854 | 233/861 | 1.03 (0.86, 1.23) |
| | Rectum | 30/114 | 36/112 | 1.29 (0.79, 2.09) |
| Stage | III | 180/595 | 195/602 | 1.07 (0.87, 1.31) |
| | II | 76/373 | 74/371 | 1.01 (0.73, 1.39) |
| Gender | Female | 101/414 | 100/418 | 0.87 (0.66, 1.15) |
| | Male | 155/554 | 169/555 | 1.10 (0.89, 1.37) |

  - DFS in patients with MSS (n=840): HR* 1.43 (CI 1.12, 1.84); p=005
  - DFS in patients with MSI (n=135): HR* 0.74 (CI 0.35, 1.56); p=0.42
- **Conclusions**
  - **Capecitabine + bevacizumab provided no additional benefit to capecitabine alone in patients with CRC post R0 resection**
  - **Subgroup analyses did not identify a specific subpopulation to benefit from the addition of bevacizumab**
  - **Patients with MSS had a reduced DFS when treated with capecitabine + bevacizumab compared with capecitabine alone**

*Capecitabine alone vs. capecitabine + bevacizumab

Midgley et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA12

# 502PD: MOSAIC study: Actualization of overall survival (OS) with 10 years follow up and evaluation of BRAF. By GERCOR and MOSAIC investigators – André T et al.

- **Study objective**
  - To report the 10-year follow-up and *BRAF* evaluable population results for the MOSAIC* study
- **Study design**
  - Of the 2,246 patients included in MOSAIC study, actualisation of survival was carried out at 10-year follow-up
  - FFPE samples for *BRAF* mutation testing were available in 903 patients
    - Testing was conducted using a pre-amplification method followed by Amplification Refractory Mutation System technology
    - 15 variables were evaluated in univariate and multivariate analysis of prognostic factors for DFS in the *BRAF* evaluable population

*Patients with stage II/III colon cancer were randomised to receive fluorouracil + leucovorin ± oxaliplatin after curative resection (N=2246)

André et al. Ann Oncol 2014; 25 (suppl 4); abstr 502PD

# 502PD: MOSAIC study: Actualization of Overall Survival (OS) with 10 years follow up and evaluation of BRAF. by GERCOR and MOSAIC investigators – André T et al.

- **Key results**

| | | FOLFOX4 vs. LV5FU | | | |
|---|---|---|---|---|---|
| **OS at 10-year follow-up** | **N** | **Absolute difference, %** | **HR** | **CI** | **p-value** |
| Stage II and III | 2,246 | 4.6 | 0.85 | 0.73, 0.99 | 0.043 |
| Stage III | 1,347 | 8.1 | 0.80 | 0.66, 0.96 | 0.015 |
| Stage IIIC | 1,347 | 13.2 | 0.70 | 0.53, 0.92 | 0.01 |

  - *BRAF* wt: 78.8%; *BRAF* mut: 9.1%; pMMR 88.6%; dMMR 9.3%
  - *BRAF* was not a prognostic factor
    - 5-year RFI: mut 73.1 vs. wt 72.5 (HR 0.97 [95% CI 0.65, 1.44]; p=0.863)

| **DFS at 10 years** | | **N** | **Events** | **HR*** | **CI** | **p-value** |
|---|---|---|---|---|---|---|
| MMR | dMMR | 85 | 20 | 1.00 | | |
| | pMMR | 815 | 318 | 1.81 | 1.27, 2.57 | 0.009 |
| *BRAF* | wt | 809 | 307 | 1.00 | | |
| | mut | 94 | 33 | 0.96 | 0.67, 1.36 | 0.818 |

*Univariate analysis
RFI, relapse-free interval

André et al. Ann Oncol 2014; 25 (suppl 4): abstr 502PD

# 502PD: MOSAIC study: Actualization of Overall Survival (OS) with 10 years follow up and evaluation of BRAF. by GERCOR and MOSAIC investigators – André T et al.

- **Key results (cont.)**

| OS at 10-years | N | FOLFOX4 | LV5FU | HR | 95% CI | p-value |
|---|---|---|---|---|---|---|
| *BRAF* mut, months | 94 | 75.8 | 65.7 | 0.66 | 0.31, 1.41 | 0.287 |
| *BRAF* wt, months | 809 | 70.3 | 68.4 | 0.94 | 0.73, 1.20 | 0.599 |

- **Conclusions**
  - **After 10 years' follow-up, the benefit of oxaliplatin as an adjuvant therapy for stage II/III colon cancer was confirmed for DFS and OS**
    - **Absolute OS difference has increased from 2.1% (5 years) to 4.6%**
  - **dMMR is a prognostic factor, but not *BRAF***
  - **FOLFOX benefitted patients with dMMR status and those with *BRAF* mutation**

André et al. Ann Oncol 2014; 25 (suppl 4): abstr 502PD

## 503PD: A genetic response profile to predict efficacy of adjuvant 5-FU in colon cancer – Buhl I et al.

- **Study objective**
  - To validate a predictive biomarker profile for 5-FU in patients with colon cancer
- **Study design**
  - The 5-FU signature comprised 205 positively and negatively correlated genes mapped to 669 probe sets
  - The profile was tested in FFPE samples from stage III patients receiving adjuvant 5-FU* with or without irinotecan (n=636) or stage II patients not receiving adjuvant therapy (n=359)
- **Key results**

| Low vs. high 5-FU profile score | 5-FU treated patients | | Untreated patients | |
|---|---|---|---|---|
| | RFS | OS | RFS | OS |
| HR (95% CI) | 0.54 (0.41, 0.71) | 0.47 (0.34, 0.63) | 0.92 (0.64, 1.33) | 0.96 (0.67, 1.4) |
| p-value | $7.87 \times 10^{-6}$ | $7.4 \times 10^{-7}$ | 0.671 | 0.849 |

- **Conclusion**
  - **The 5-FU signature may provide predictive information regarding the response to adjuvant 5-FU therapy in patients with colon cancer**

Buhl et al. Ann Oncol 2014; 25 (suppl 4): abstr 503PD

## 504PD: Three or six months of adjuvant chemotherapy for colon cancer: Compliance and safety of the phase III Italian TOSCA trial – Lonardi S et al.

- **Study objective**
  - Non-inferiority phase III trial comparing 3 vs. 6 months of adjuvant FOLFOX4 or XELOX in patients with stage III or high-risk stage II colon cancer
- **Study design**
  - 3,720 patients were randomised to 3 months (n=1,850) or 6 months (n=1,870) treatment with adjuvant FOLFOX4 or XELOX
- **Key results**
  - Proportion of patients completing trial: 68% for 6 months vs. 91% for 3 months

| Grade 3/4 AEs, % | 6 months | 3 months | p-value |
|---|---|---|---|
| Febrile neutropenia | 2.7 | 1.4 | 0.004 |
| Asthenia | 4.1 | 1.2 | <0.0001 |
| Allergic reaction | 1.9 | 0.5 | <0.0001 |
| Neurotoxicity | 31.2 | 8.8 | <0.0001 |

- **Conclusions**
  - **Toxicity was generally low but higher in the 6-month vs. 3-month arm**
  - **Efficacy analysis is ongoing**

*AEs with significant differences are listed

Lonardi et al. Ann Oncol 2014; 25 (suppl 4): abstr 504PD

## LBA14: Molecular subtype and chemotherapy-related toxicity in stage 3 colon cancers: NCCTG N0147 – Sinicrope F et al.

- **Study objective**
  - A post-hoc analysis to investigate the association between molecular subtypes and AEs in patients with stage 3 colon cancer receiving FOLFOX ± cetuximab
- **Study design**
  - Tumours were categorised by DNA mismatch repair (dMMR) status and mutually exclusive *BRAF* or *KRAS* mutations
  - Associations between subtypes and grade ≥3 AEs was determined by Chi-squared test and logistic regression
- **Key results**
  - Overall 77% of patients in the sporadic dMMR subtype completed >6 treatment cycles vs. 87–91% of patients in other subtypes (p=0.029)
  - Overall grade ≥3 AEs among patients receiving <12 cycles was highest for sporadic dMMR (81%) and lowest for familial dMMR (40%) subtypes (p=0.016)
  - For distal, but not proximal, cancers, dMMR patients had the highest AE rate (78%)
  - Mutant $BRAF^{V600E}$ proficient MMR had the lowest AE rate (33%)
- **Conclusion**
  - **Sporadic dMMR patients had fewer treatment cycles and greater toxicity**

Sinicrope et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA14

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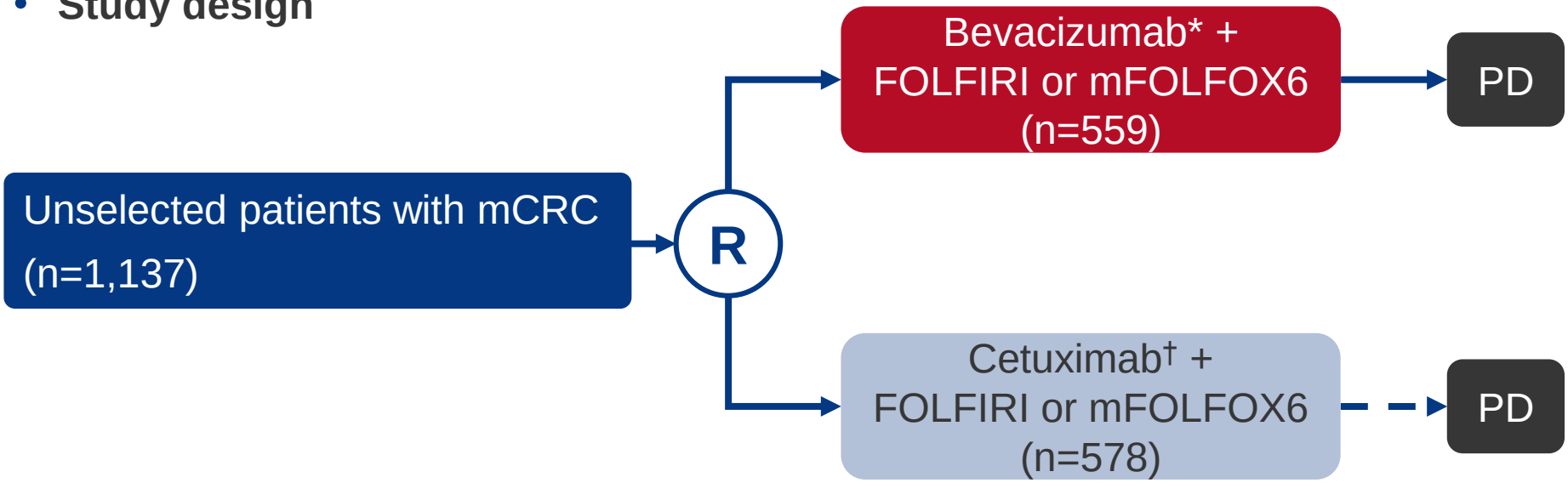
# FIRST-LINE THERAPY

# 501O: 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 expanded ras analyses untreated metastatic adenocarcinoma of the colon – Lenz H et al.

- **Study objective**
  - Post-hoc analysis assessing expanded *RAS* in patients with mCRC treated with first-line bevacizumab vs. cetuximab in combination with either FOLFIRI or mFOLFOX6
- **Study design**



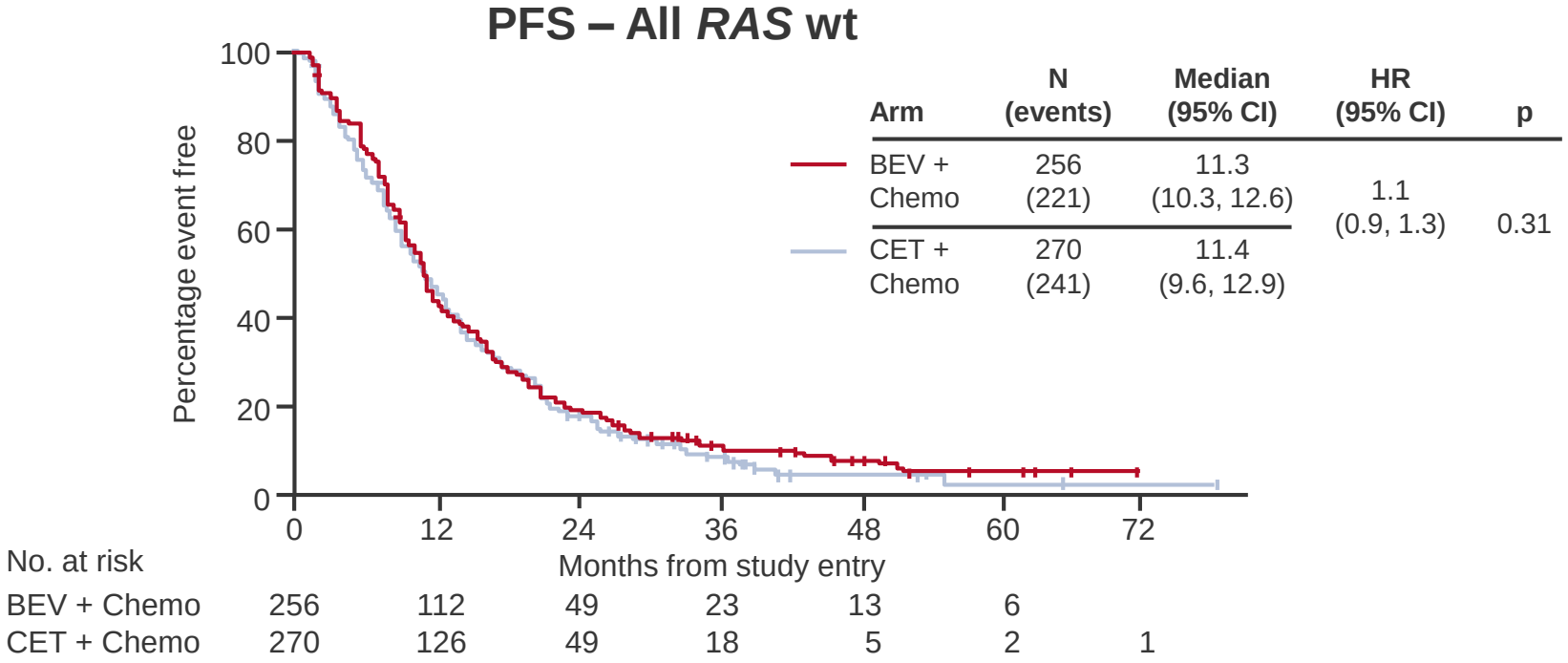

***RAS* evaluable patients: Bevacizumab n=324 vs. cetuximab n=346**

*5 mg/kg q2w; †400 mg/m$^2$ x1, then 250 mg/m$^2$ qw

Lenz H et al. Ann Oncol 2014; 25 (suppl 4): abstr 501O

# 501O: 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 expanded ras analyses untreated metastatic adenocarcinoma of the colon – Lenz H et al.

- **Key results**




| PFS by chemotherapy (All *RAS* wt patients) | Bevacizumab + chemotherapy | Cetuximab + chemotherapy | HR (95% CI) | p-value |
|---|---|---|---|---|
| FOLFOX | 11.0 months | 11.3 months | 1.1 (0.9, 1.4) | 0.3 |
| FOLFIRI | 11.9 months | 12.7 months | 1.1 (0.7, 1.5) | 0.7 |

Lenz H et al. Ann Oncol 2014; 25 (suppl 4): abstr 501O

# 501O: 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 expanded ras analyses untreated metastatic adenocarcinoma of the colon – Lenz H et al

- **Key results (cont.)**

| Subgroup | BEV + Chemo N | CET + Chemo N | BEV + Chemo vs. CET + Chemo | | |
|---|---|---|---|---|---|
| | | | RR (%) | mPFS (months) | mOS (months) |
| *KRAS* codon 12/13 wt | 559 | 578 | 57.2 vs. 65.6 | 10.8 vs. 10.4 | 29.0 vs. 29.9 |
| HR (95% CI) | | | - | 1.04 (0.91, 1.17) | 0.92 (0.78, 1.09) |
| p-value | | | 0.02 | 0.55 | 0.34 |
| *RAS* evaluable* | 324 | 346 | 56.0 vs. 68.8 | 11.4 vs. 10.9 | 30.3 vs. 30.8 |
| HR (95% CI) | | | - | 1.10 (0.90, 1.30) | 0.90 (0.70, 1.10) |
| p-value | | | <0.01 | 0.31 | 0.40 |

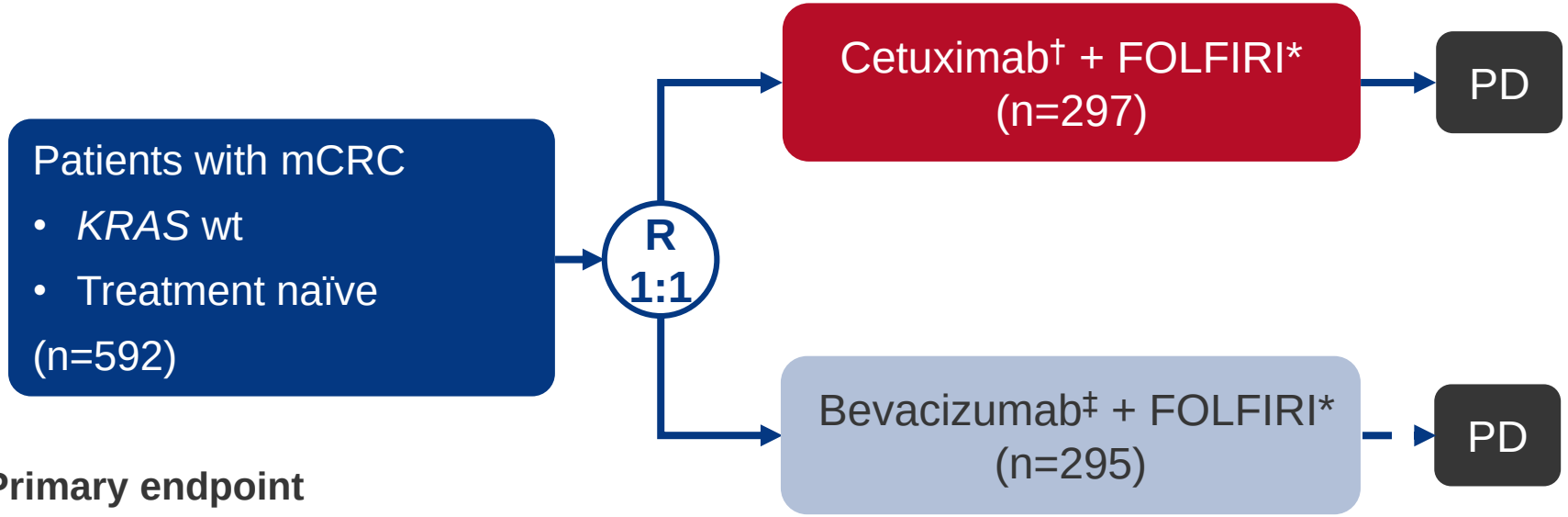
- **Conclusions**
  - **All patients with newly diagnosed mCRC should be tested for *RAS***
  - **Overall survival of >30 months in both treatment groups sets a new benchmark for patients with mCRC**

*Patients with *KRAS* codon 12/13 wt tumours evaluable for other *RAS* mutations

Lenz H et al. Ann Oncol 2014; 25 (suppl 4): abstr 501O

# LBA11: Independent radiological evaluation of objective response, early tumor shrinkage, and depth of response in FIRE-3 (AIO KRK-0306) in the final RAS evaluable population – Stintzing S et al.

- **Study objective**
  - *RAS* analysis and independent radiological review to assess tumour response and early tumour shrinkage in patients with *KRAS* exon 2 wt mCRC treated with either cetuximab or bevacizumab plus FOLFIRI as first-line therapy




**Primary endpoint**

- **ORR (RECIST 1.0)**

**Response evaluable (RECIST) 83%: Cetuximab + FOLFIRI (n=236) vs. Bevacizumab + FOLFIRI (n=257)**

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

Stintzing et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA11

# LBA11: Independent radiological evaluation of objective response, early tumor shrinkage, and depth of response in FIRE-3 (AIO KRK-0306) in the final RAS evaluable population – Stintzing S et al.

- **Key results**
  ***RAS* analysis**:

| Cetuximab + FOLFIRI vs. Bevacizumab + FOLFIRI | *RAS* wt population | | *RAS* mut population | |
|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| ORR | 1.33 (0.88, 1.99) | 0.18 | 0.60 (0.34, 1.08) | 0.11 |
| mPFS | 0.97 (0.78, 1.20) | 0.77 | 1.25 (0.93, 1.68) | 0.14 |
| mOS | 0.70 (0.54, 0.90) | 0.0059 | 1.05 (0.77, 1.44) | 0.75 |

**Independent radiological review**:

– ITT population: ORR (cetuximab vs. bevacizumab) HR 1.18 (0.85, 1.64), p=0.183

| Cetuximab + FOLFIRI vs. Bevacizumab + FOLFIRI | *KRAS* exon 2 wt | | Final *RAS* wt | |
|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| ORR | 1.58 (1.10, 2.28) | 0.016 | 2.01 (1.27, 3.19) | 0.003 |
| Early tumour shrinkage | 1.80 (1.26, 2.58) | 0.0015 | 2.22 (1.41, 3.47) | 0.0005 |

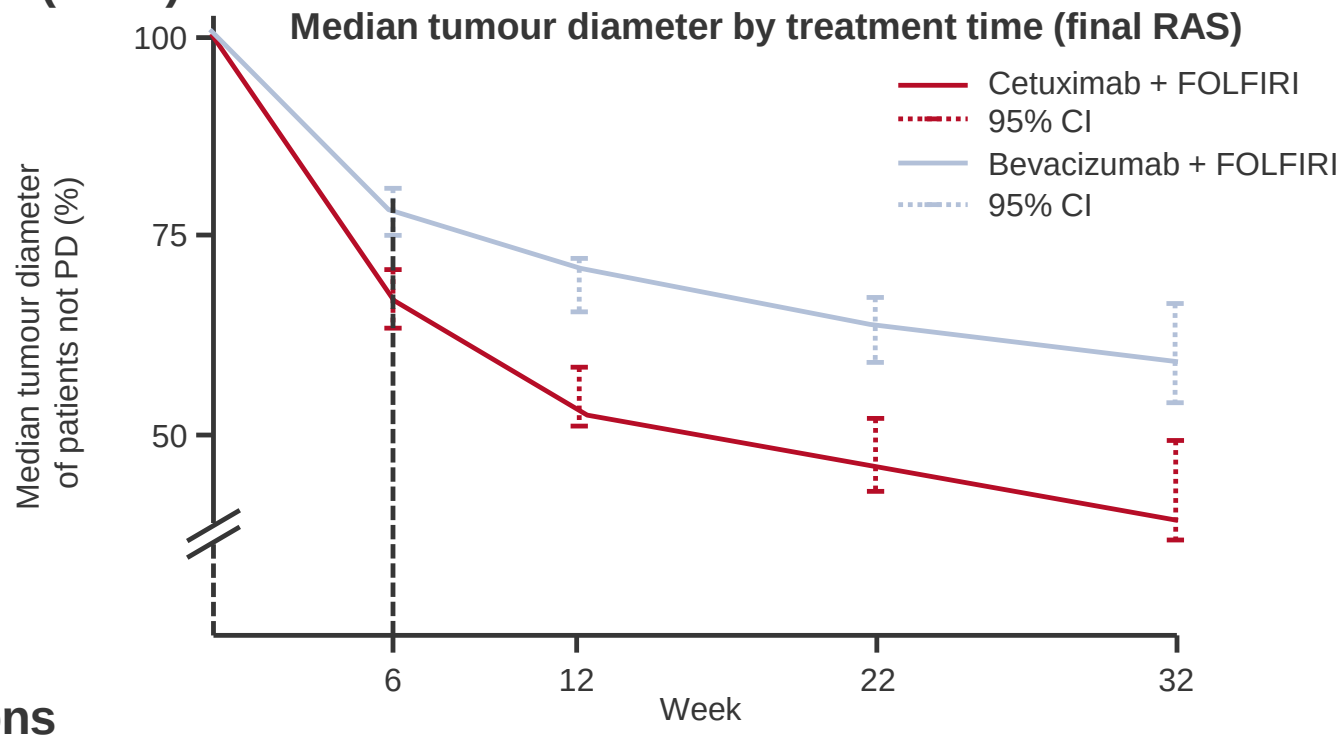
– Early tumour shrinkage correlated with PFS in the cetuximab arm (p=0.0037) and OS in the cetuximab and bevacizumab arm (p=0.0023 vs. p=0.0001, respectively)

– Depth of response (RAS wt): –48.9% cetuximab arm vs. –32.3% bevacizumab arm (p<0.0001); depth of response correlated with OS and PFS

Stintzing et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA11

# LBA11: Independent radiological evaluation of objective response, early tumor shrinkage, and depth of response in FIRE-3 (AIO KRK-0306) in the final RAS evaluable population – Stintzing S et al.

- **Key results (cont.)**




- **Conclusions**
  - **The RAS evaluable population was comparable to the ITT population**
  - **The independent radiological review demonstrated that cetuximab + FOLFIRI significantly improved ORR, early tumour shrinkage and depth of response compared with bevacizumab + FOLFIRI**

Stintzing et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA11

## 509PD: Primary tumour location (PTL) as a prognostic and predictive factor in advanced colorectal cancer (aCRC): Data from 2075 patients (pts) in randomised trials – Seligmann J et al.

- **Study objective**
  - To investigate whether primary tumour location has an impact on tumour biology, survival and response to treatment in patients with advanced CRC
- **Study design**
  - Data from 2,075 patients from the FOCUS and PICCOLO trials were analysed to compare primary tumour location: right colon vs. left colon or rectum (primary analysis) or left colon vs. rectum
- **Key results**
  - Right colon tumours were associated with worse OS in first-line (HR 1.44; p=0.001) but not second-line treatment (HR 1.13; p=0.31) vs. left colon tumours
  - Left colon tumours had improved OS in first-line (HR 0.75; p=0.015) and second-line (HR 0.76; p=0.05) vs. rectal tumours
  - Primary tumour location did not predict OS or PFS benefit from upfront doublet vs. single agent FU
- **Conclusions**
  - **Right colon tumours were biologically distinct and had worse OS in the first-line setting vs. left colon tumours**
  - **Primary tumour location is not recommended as a predictive biomarker**

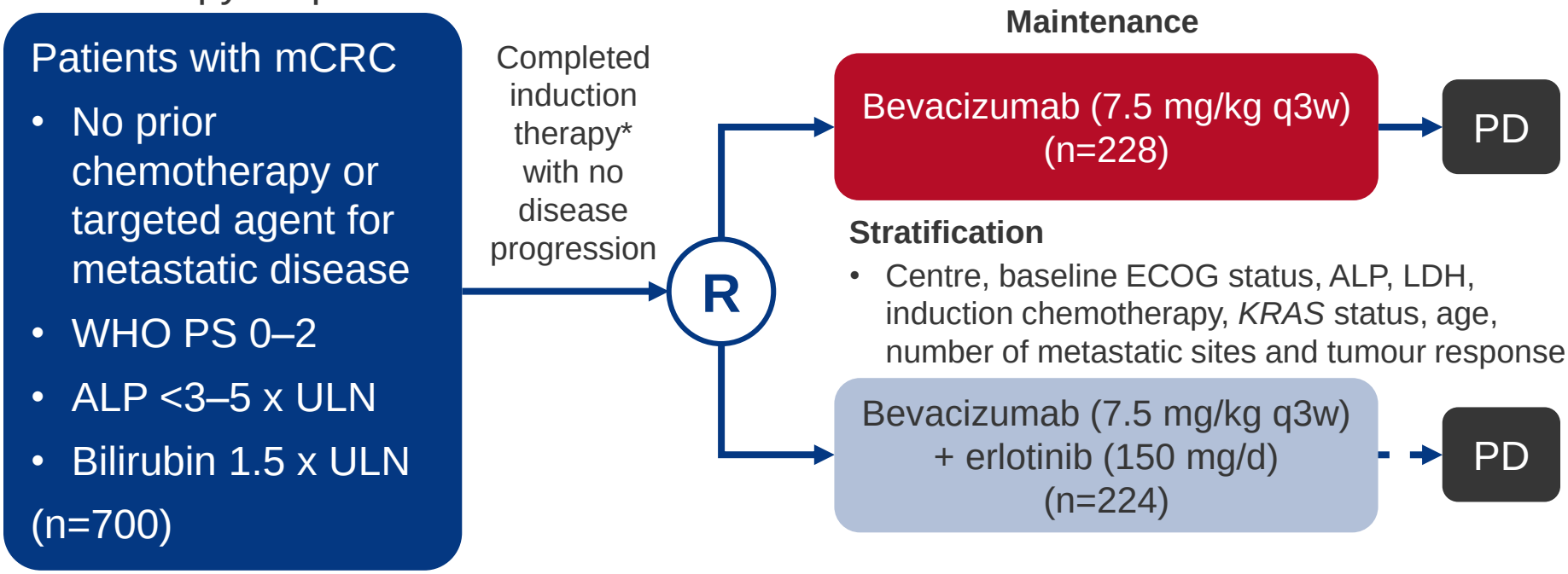
Seligmann et al. Ann Oncol 2014; 25 (suppl 4): abstr 509PD

COLORECTAL CANCER

# MAINTENANCE

# 497O: Bevacizumab-erlotinib as maintenance therapy in metastatic colorectal cancer. Final results of the GERCOR DREAM study – Chibaudel B et al.

- **Study objective**
  - Phase III trial to assess the efficacy and safety of erlotinib in combination with bevacizumab as maintenance therapy following bevacizumab-based induction therapy* in patients with unresectable mCRC




**Primary endpoint**
- PFS on maintenance

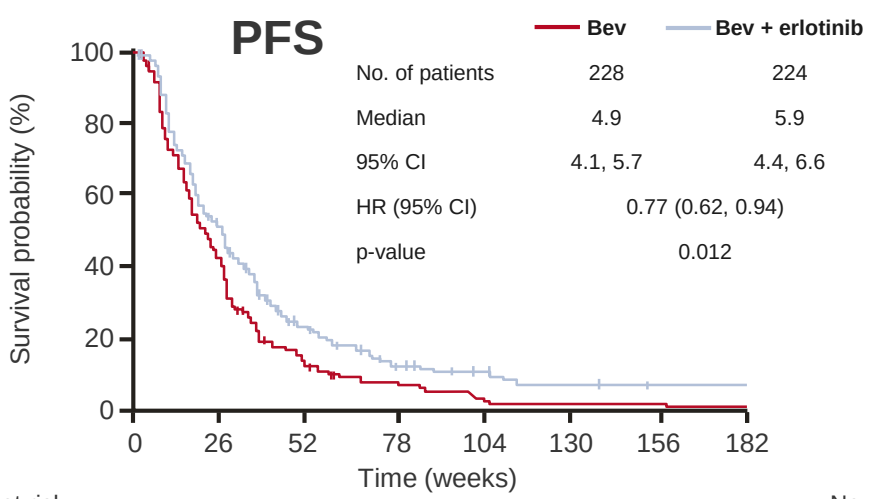
**Secondary endpoints**
- OS, PFS from registration, RR, safety, HRQoL

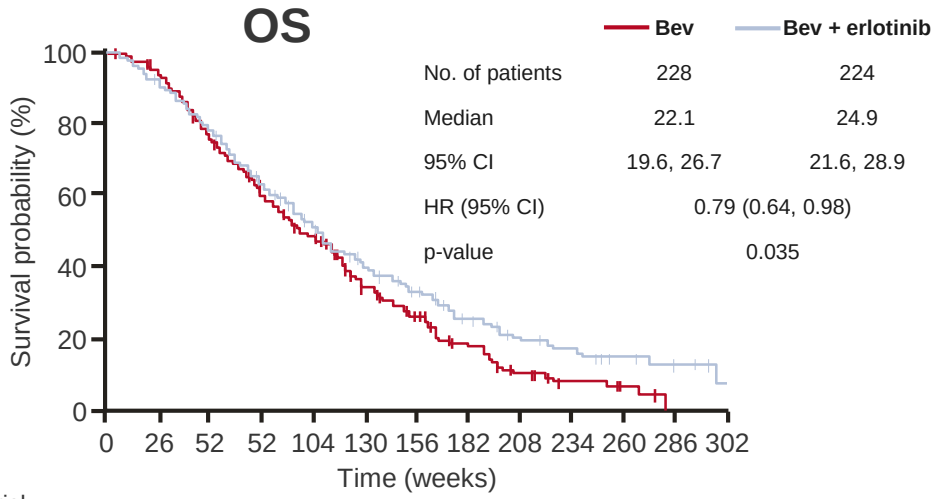
*Bevacizumab plus mFOLFOX7, mXELOX2 or FOLFIRI

Chibaudel et al. Ann Oncol 2014; 25 (suppl 4): abstr 497O

# 497O: Bevacizumab-erlotinib as maintenance therapy in metastatic colorectal cancer. Final results of the GERCOR DREAM study – Chibaudel B et al.

- **Key results**




| | All patients | | wt *KRAS* | | Mutant *KRAS* | |
|---|---|---|---|---|---|---|
| | **Bev** | **Bev + erlotinib** | **Bev** | **Bev + erlotinib** | **Bev** | **Bev + erlotinib** |
| **ORR** | 11.5 | 22.5 | 15.4 | 24.0 | 8.3 | 19.7 |
| **p-value** | | 0.003 | | 0.133 | | 0.041 |

Chibaudel et al. Ann Oncol 2014; 25 (suppl 4): abstr 4970

# 497O: Bevacizumab-erlotinib as maintenance therapy in metastatic colorectal cancer. Final results of the GERCOR DREAM study – Chibaudel B et al.

- **Key results (cont.)**

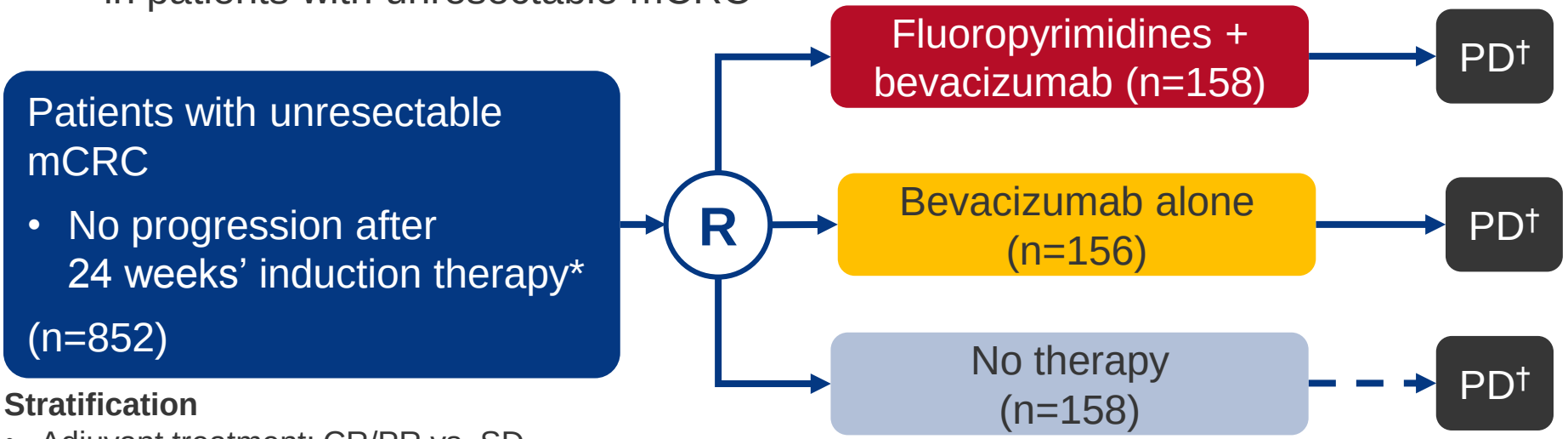
| CTCAE Term, % | Bevacizumab (n=228) | Bevacizumab + erlotinib (n=224) | p-value |
|---|---|---|---|
| Neutrophils | 10 | 13 | 0.211 |
| Platelets | 20 | 16 | 0.556 |
| Haemoglobin | 30 | 31 | 0.613 |
| Nausea | 8 | 17 | 0.025 |
| Vomiting | 6 | 10 | 0.355 |
| Mucositis | 4 | 13 | 0.012 |
| Diarrhoea | 14 | 59 | <0.001 |
| Skin rash | 9 | 89 | <0.001 |
| Proteinuria | 24 | 35 | 0.026 |

- **Conclusions**
  - **Bevacizumab + erlotinib maintenance significantly prolonged PFS and OS vs. bevacizumab alone in patients with unresectable mCRC**
    - **This observation was present even in patients with mutated *KRAS***
  - **There was also a significant difference in ORR in *KRAS* mutated tumours**
  - **Safety was acceptable despite an increased incidence of skin rash and diarrhoea**

Chibaudel et al. Ann Oncol 2014; 25 (suppl 4): abstr 4970

# 498O: Maintenance strategy with fluoropyrimidines (FP) plus bevacizumab (Bev), Bev alone or no treatment, following a 24-week first-line induction with FP, oxaliplatin (Ox) and Bev for patients with metastatic colorectal cancer: Mature data and subgroup analysis of the AIO KRK 0207 phase III study – Hegewisch-Becker S et al.

- **Study objective**
  - To evaluate whether either no treatment or bevacizumab alone was non-inferior to fluoropyrimidines (FP) plus bevacizumab, after 24-weeks' induction therapy* in patients with unresectable mCRC




**Stratification**
- Adjuvant treatment; CR/PR vs. SD, ECOG PS; CEA at baseline

**Primary endpoint**
- TFS (at first or second progression)

**Secondary endpoints**
- PFS-1, OS
- Toxicity, QoL, biomarkers

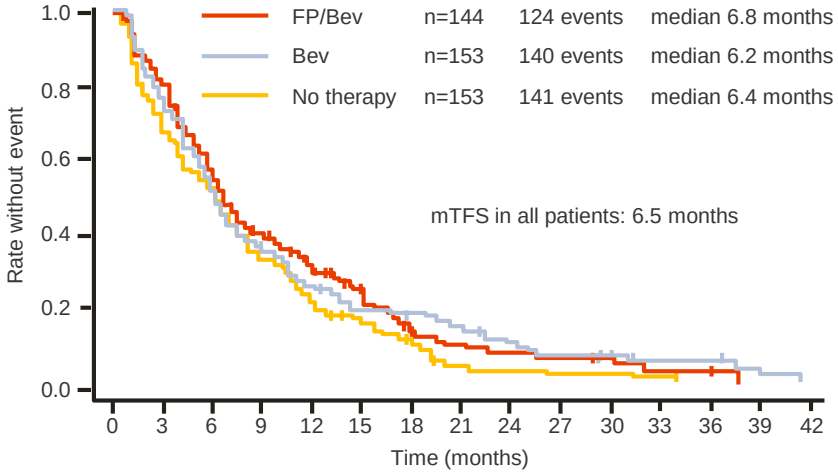
*Fluoropyrimidines/oxaliplatin/bevacizumab; †Re-induction of any of the initial treatments at first progression
TFS, time to failure of strategy

Hegewisch-Becker et al. Ann Oncol 2014; 25 (suppl 4): abstr 498O

# 498O: Maintenance strategy with fluoropyrimidines (FP) plus bevacizumab (Bev), Bev alone or no treatment, following a 24-week first-line induction with FP, oxaliplatin (Ox) and Bev for patients with metastatic colorectal cancer: Mature data and subgroup analysis of the AIO KRK 0207 phase III study – Hegewisch-Becker S et al.

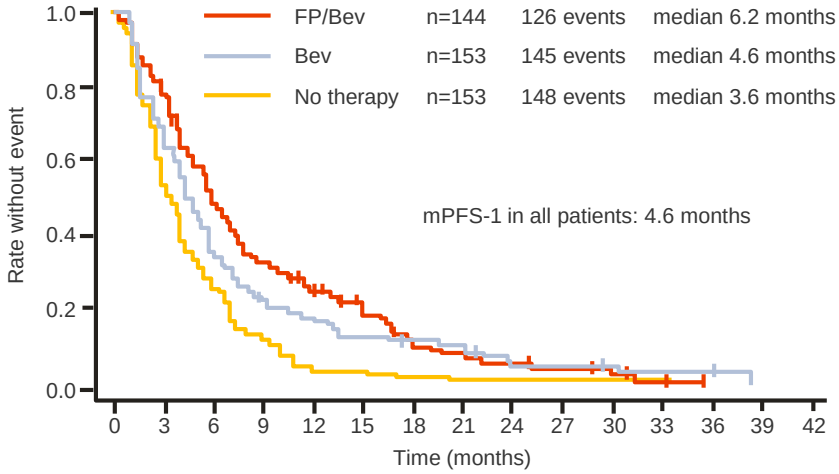
- **Key results**

## TFS




**FP/Bev vs. Bev**: HR 1.03 (95% CI 0.81, 1.31); p=0.82
**FP/Bev vs. no therapy**: HR 1.27 (95% CI 1.00, 1.62); p=0.054

## PFS-1



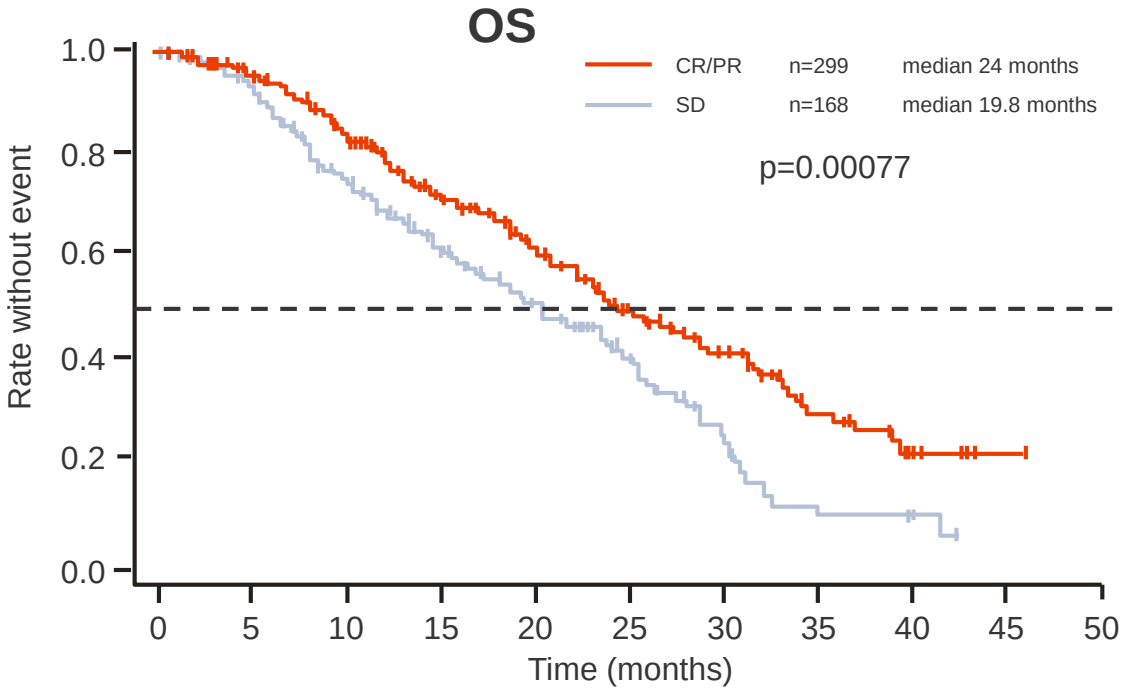

**FP/Bev vs. Bev**: HR 1.26 (95% CI 0.99, 1.60); p=0.061
**FP/Bev vs. no therapy**: HR 2.05 (95% CI 1.61, 2.63); p<0.00001
**Bev vs. no therapy**: HR 1.53 (95% CI 1.21, 1.93); p=0.00039

- Overall survival:
  - 23.4 months with fluoropyrimidines + bevacizumab vs. 22.6 months with bevacizumab alone and 23.3 months with no therapy (p=NS between the groups)

Hegewisch-Becker et al. Ann Oncol 2014; 25 (suppl 4): abstr 498O

# 498O: Maintenance strategy with fluoropyrimidines (FP) plus bevacizumab (Bev), Bev alone or no treatment, following a 24-week first-line induction with FP, oxaliplatin (Ox) and Bev for patients with metastatic colorectal cancer: Mature data and subgroup analysis of the AIO KRK 0207 phase III study – Hegewisch-Becker S et al.

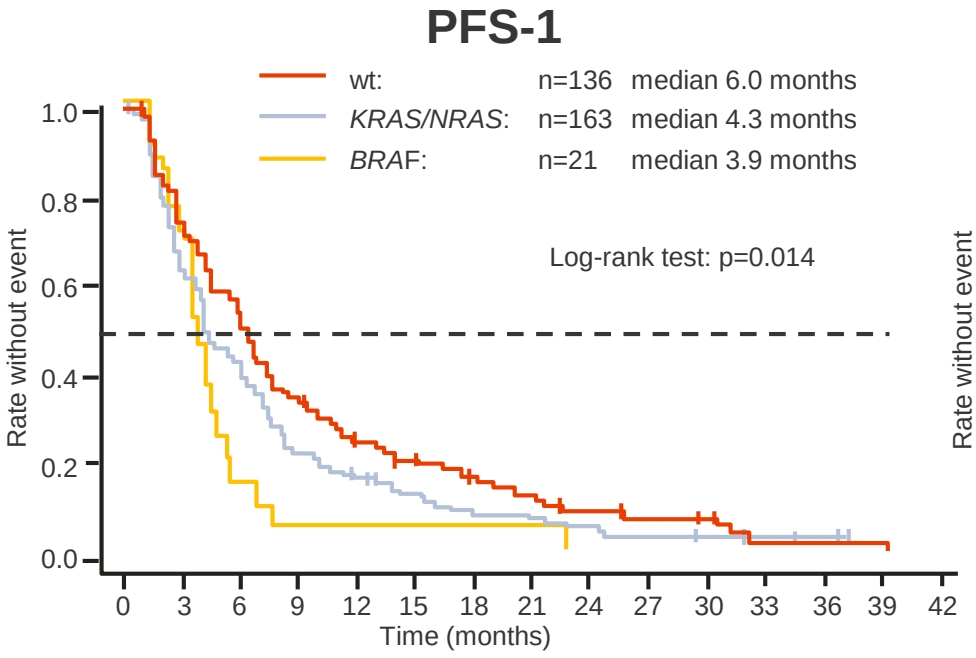
- **Key results (cont.)**
  - Oxaliplatin dose reduction during induction did not impact PFS-1 or OS
    - mPFS-1: 4.3 months with no reduction vs. 4.8 months with reduction (p=0.63)
    - mOS: 22.7 months with no reduction vs. 23.7 months with reduction (p=0.35)
  - Patients with the best response at induction (CR/PR) had improved OS vs. SD

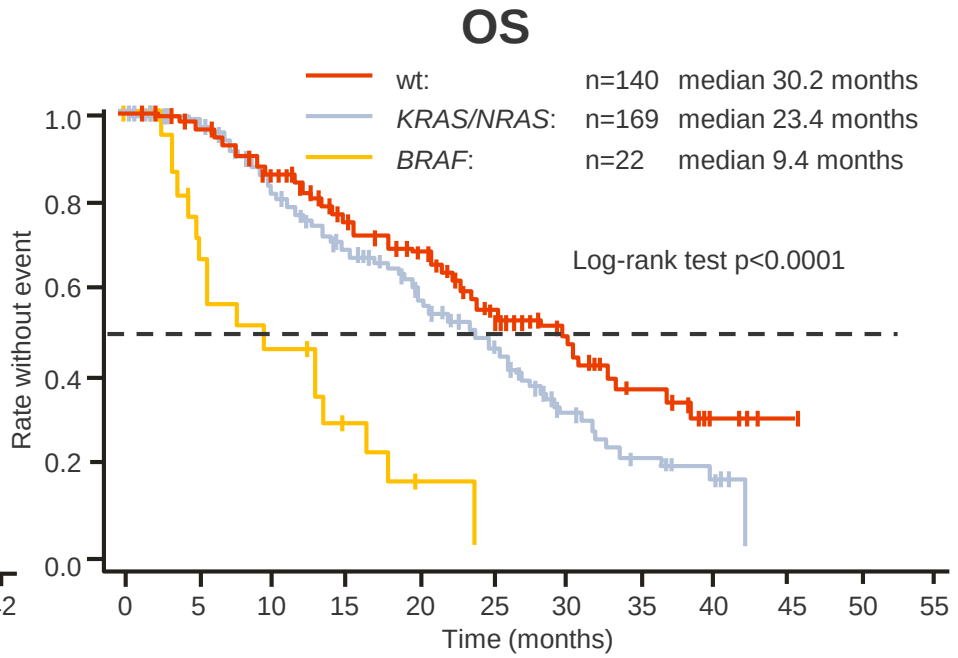



Hegewisch-Becker et al. Ann Oncol 2014; 25 (suppl 4): abstr 498O

# 498O: Maintenance strategy with fluoropyrimidines (FP) plus bevacizumab (Bev), Bev alone or no treatment, following a 24-week first-line induction with FP, oxaliplatin (Ox) and Bev for patients with metastatic colorectal cancer: Mature data and subgroup analysis of the AIO KRK 0207 phase III study – Hegewisch-Becker S et al.

- **Key results (cont.)**
  - Mutation status showed: 39% wild type, 52% *RAS* mutant and 9% *BRAF* mutant
  - PFS-1 and OS were longer in patients with wild type status vs. *RAS* or *BRAF* mutations




  - Improved PFS-1 with active vs. no treatment was maintained in all subgroups analysed, with no patient group with identified that had greater or lesser benefit

Hegewisch-Becker et al. Ann Oncol 2014; 25 (suppl 4): abstr 498O

## 498O: Maintenance strategy with fluoropyrimidines (FP) plus bevacizumab (Bev), Bev alone or no treatment, following a 24-week first-line induction with FP, oxaliplatin (Ox) and Bev for patients with metastatic colorectal cancer: Mature data and subgroup analysis of the AIO KRK 0207 phase III study – Hegewisch-Becker S et al.

- **Conclusions**
  - **Bevacizumab maintenance was non-inferior to fluoropyrimidines + bevacizumab for TFS**
    - **No active treatment was inferior to fluoropyrimidines + bevacizumab**
  - **Significant improvement in PFS-1, but not OS, with active treatment**
  - **Response to induction and *RAS* status had a prognostic impact, whereas oxaliplatin dose reduction did not**
  - **The benefit with active maintenance on PFS-1 remains significant in all subgroups analysed**
    - **In contrast to the CAIRO-3 study, subgroup analyses did not identify a patient group with a greater or lesser benefit of fluoropyrimidines + bevacizumab maintenance therapy**

Hegewisch-Becker et al. Ann Oncol 2014; 25 (suppl 4): abstr 498O

# 499O: Phase II study of first-line mFOLFOX plus cetuximab (C) for 8 cycles followed by mFOLFOX plus C or single agent (s/a) C as maintenance therapy in patients (p) with metastatic colorectal cancer (mCRC): The MACRO-2 trial (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD]) – García Alfonso P et al.

- **Study objective**
  - To assess the efficacy and safety of mFOLFOX + cetuximab then maintenance mFOLFOX + cetuximab vs. cetuximab alone in treatment naïve patients with mCRC
- **Study design**
  - Patients with wt *KRAS* mCRC were randomised to mFOLFOX + cetuximab then maintenance mFOLFOX + cetuximab (n=129) or cetuximab alone (n=64)
- **Key results**

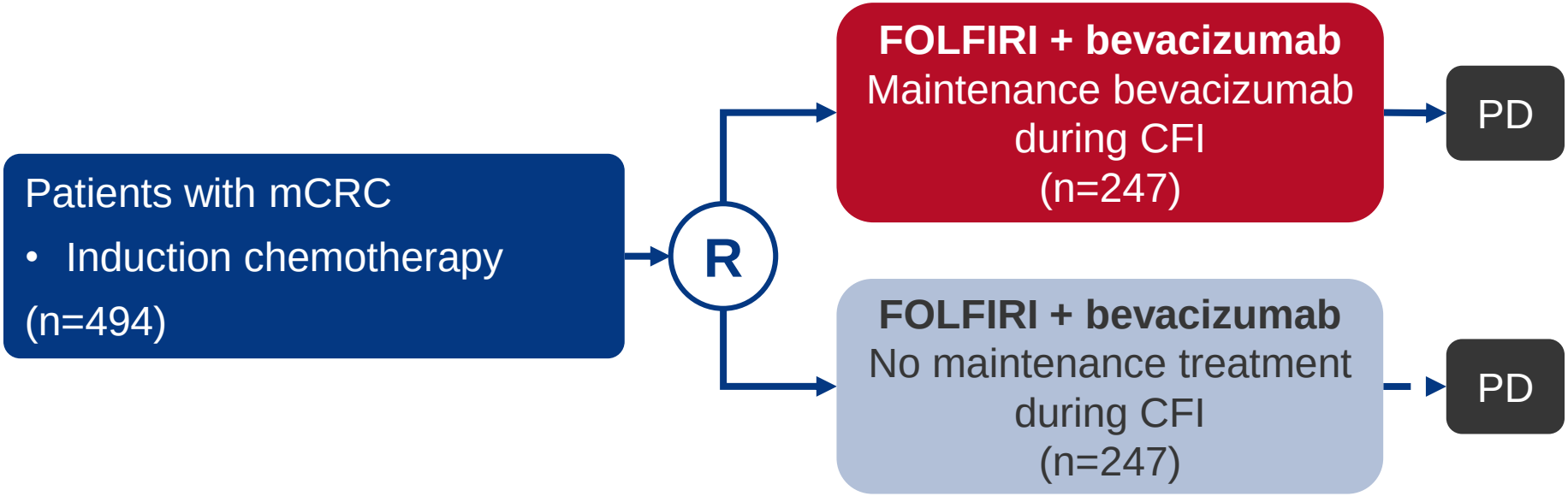
| | mFOLFOX + cetuximab | Cetuximab alone | HR (95% CI) |
|---|---|---|---|
| mPFS, months | 8.9 | 9.8 | 0.69 (0.45, 1.06) |
| mOS, months | 23.6 | 22.2 | 1.51 (0.73, 1.81) |
| ORR, % | 47 | 39 | 1.36 (0.74, 2.50) |
| PFS at 9-months, % | 64 | 72 | 0.68 (0.36, 1.31) |

  - Preliminary analysis suggests tolerability was acceptable in both arms
- **Conclusion**
  - **After mFOLFOX + cetuximab induction therapy, maintenance therapy with cetuximab alone was non-inferior to continuation of mFOLFOX + cetuximab**

García Alfonso et al. Ann Oncol 2014; 25 (suppl 4): abstr 4990

# 506PD: Interim analysis of PRODIGE 9, a randomized phase III trial comparing no treatment to bevacizumab maintenance during chemotherapy-free intervals in metastatic colorectal cancer – Aparicio T et al.

- **Study objective**
  - To compare the tumour control duration (TCD)* by first-line chemotherapy† followed by either bevacizumab maintenance or no maintenance treatment during CT-free interval (CFI) in patients with mCRC




**Primary endpoint**

- TCD

**Secondary endpoints**

- Dose intensity, toxicities
- PFS, TTP

*Time between randomisation and strategy failure; †12 cycles of FOLFIRI + bevacizumab, followed by a CFI until progression, then 8 further chemotherapy cycles, then a new CFI

Aparicio et al. Ann Oncol 2014; 25 (suppl 4): abstr 506PD

# 506PD: Interim analysis of PRODIGE 9, a randomized phase III trial comparing no treatment to bevacizumab maintenance during chemotherapy-free intervals in metastatic colorectal cancer – Aparicio T et al.

- **Key results**

| | Bevacizumab maintenance | No maintenance | HR | p-value |
|---|---|---|---|---|
| TCD, months | 14.3 | 13.4 | 0.98 | 0.86 |
| PFS, months | 9.2 | 8.0 | - | - |
| TTP, months | 9.43 | 8.12 | - | - |

  - Grade 3–4 AEs
    - 74% with bevacizumab maintenance vs. 71% with no maintenance therapy

- **Conclusions**
  - **No significant improvement of TCD with bevacizumab maintenance**
  - **There was a trend towards improved PFS with bevacizumab maintenance**
  - **No increase in toxicity was observed with bevacizumab maintenance**

TCD, tumour control duration

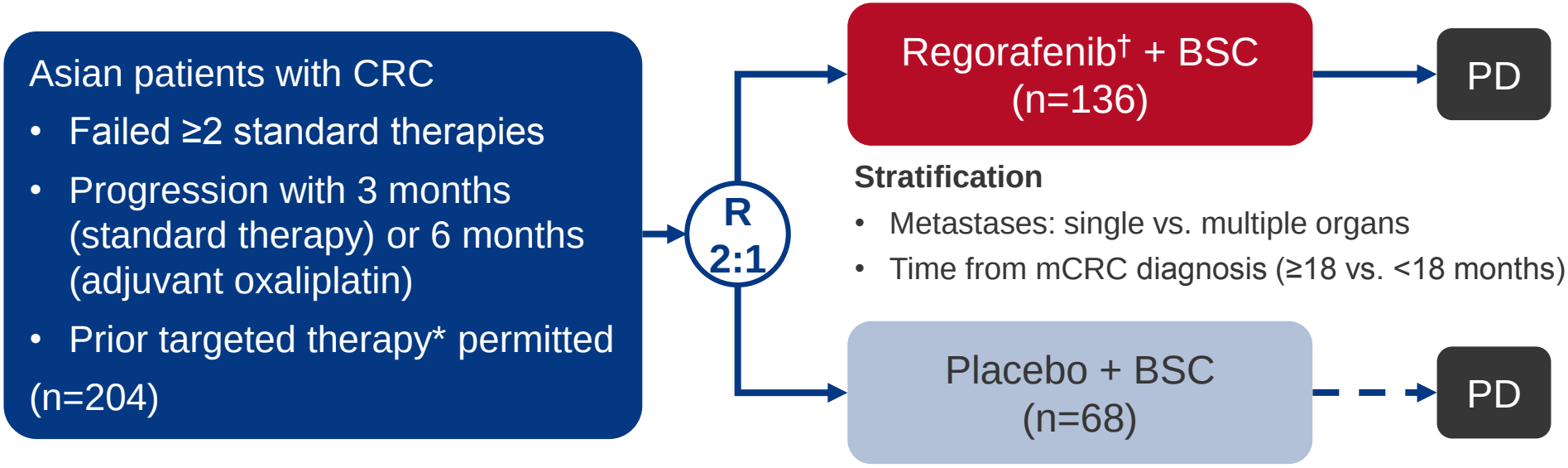
Aparicio et al. Ann Oncol 2014; 25 (suppl 4): abstr 506PD

COLORECTAL CANCER

# SECOND-LINE OR LATER THERAPY

# 500O: CONCUR: A randomized, placebo-controlled phase 3 study of regorafenib (REG) monotherapy in Asian patients with previously treated metastatic colorectal cancer (mCRC) – Kim TW et al.

- **Study objective**
  - To assess OS with regorafenib monotherapy in Asian patients with mCRC who have progressed after standard therapies




**Primary endpoint**

- OS

**Secondary endpoints**

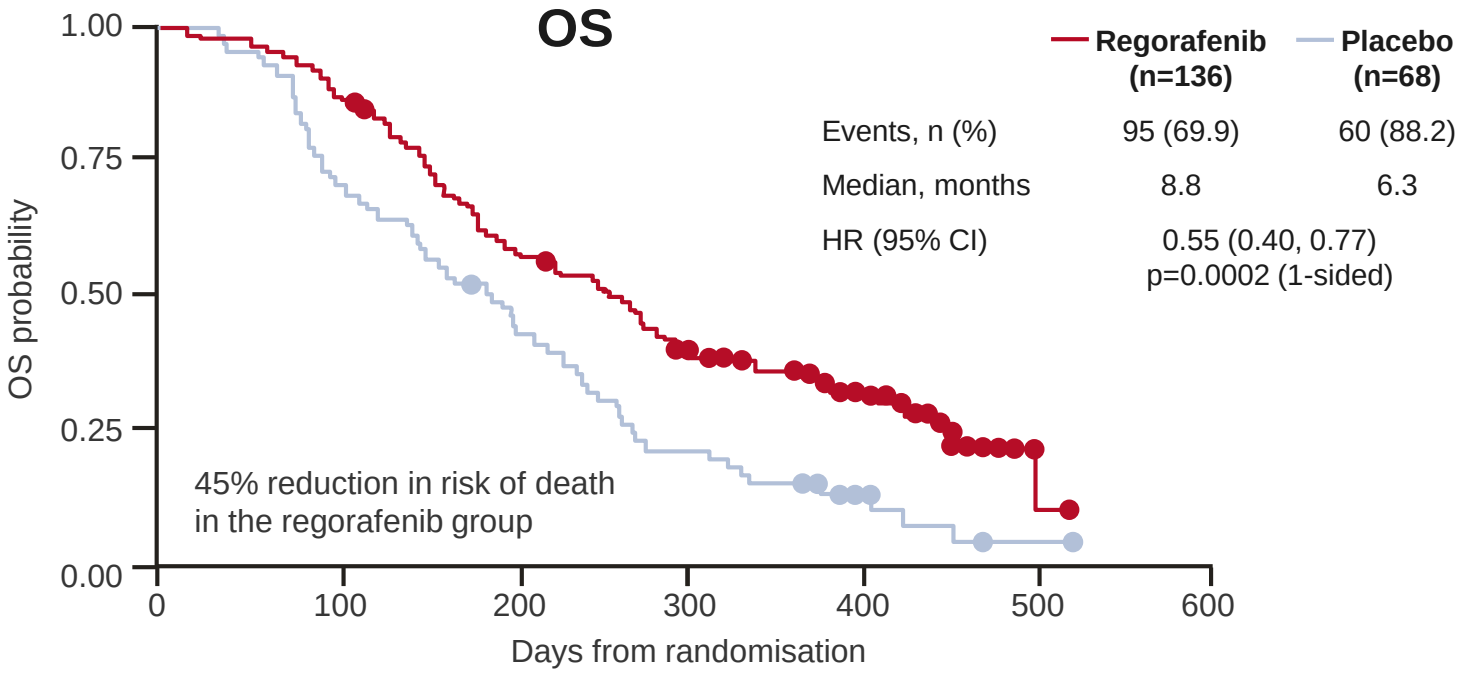
- PFS, RR, DCR

*Anti-VEGF or anti-EGFR therapy;
†160 mg/day, 3 weeks on/1 week off in 4-week cycles

Kim et al. Ann Oncol 2014; 25 (suppl 4): abstr 500O

# 500O: CONCUR: A randomized, placebo-controlled phase 3 study of regorafenib (REG) monotherapy in Asian patients with previously treated metastatic colorectal cancer (mCRC) – Kim TW et al.

- **Key results (cont.)**




| mOS by target therapy | Regorafenib N | Regorafenib mOS (months) | Placebo N | Placebo mOS (months) | HR (95% CI) |
|---|---|---|---|---|---|
| No prior targeted therapy | 56 | 9.7 | 26 | 4.9 | 0.31 (0.19, 0.53) |
| Any prior targeted therapy* | 80 | 7.4 | 42 | 6.7 | 0.78 (0.51, 1.19) |

*Anti-VEGF or anti-EGFR or both

Kim et al. Ann Oncol 2014; 25 (suppl 4): abstr 500O

## 500O: CONCUR: A randomized, placebo-controlled phase 3 study of regorafenib (REG) monotherapy in Asian patients with previously treated metastatic colorectal cancer (mCRC) – Kim TW et al.

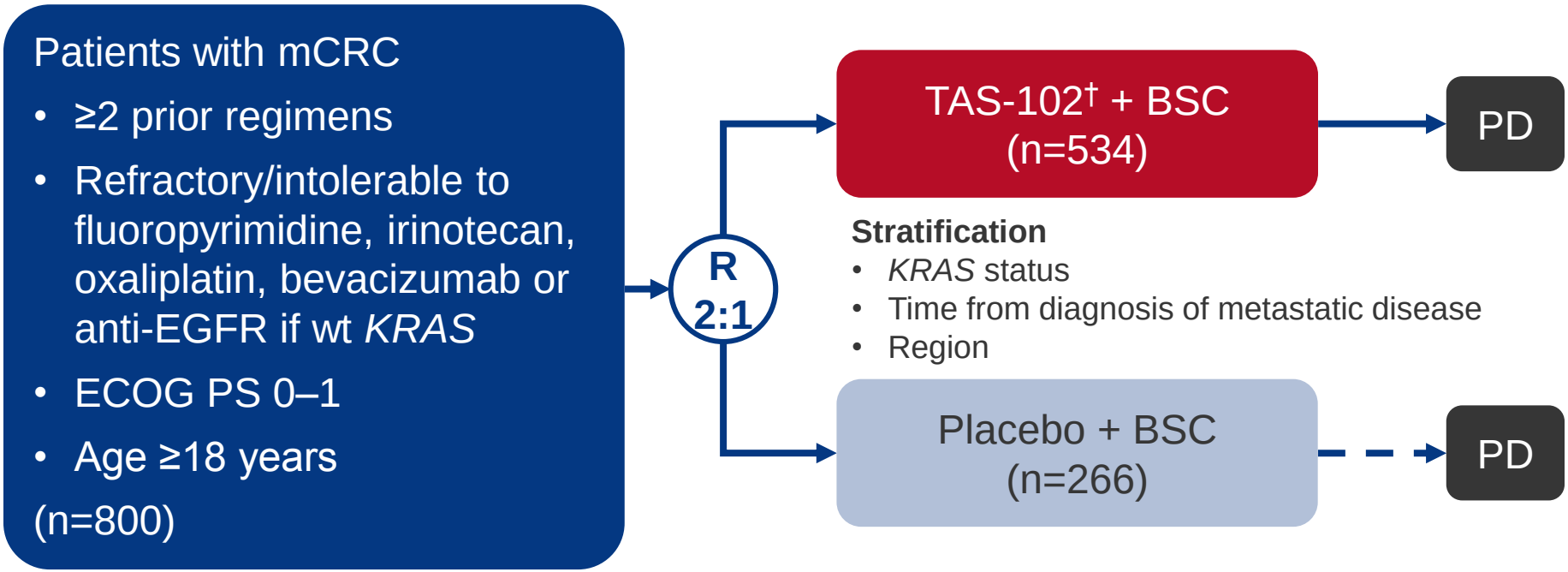
- **Key results (cont.)**
  - Most frequent grade ≥3 AEs with regorafenib:
    - Hand-foot syndrome (16%), hypertension (12%), hyperbilirubinaemia (12%), elevated liver enzymes (AST 10%, ALT 8%), hypophosphataemia (9%)
  - Permanent treatment discontinuation: regorafenib 14% vs. placebo 6%

- **Conclusions**
  - **Regorafenib significantly improved OS compared with placebo in Asian patients with mCRC**
  - **OS was longer in patients without prior anti-VEGF or anti-EGFR therapy compared with patients who had received at least one prior targeted agent**

Kim et al. Ann Oncol 2014; 25 (suppl 4): abstr 500O

# LBA13: Phase III RECOURSE trial of TAS-102 vs. placebo, with best supportive care (BSC), in patients (pts) with metastatic colorectal cancer (mCRC) refractory to standard therapies – Van Cutsem E et al.

- **Study objective**
  - To evaluate the efficacy and safety of TAS-102 vs. placebo in patients with refractory mCRC receiving best supportive care (BSC)




**Primary endpoint**

- OS

**Secondary endpoints**

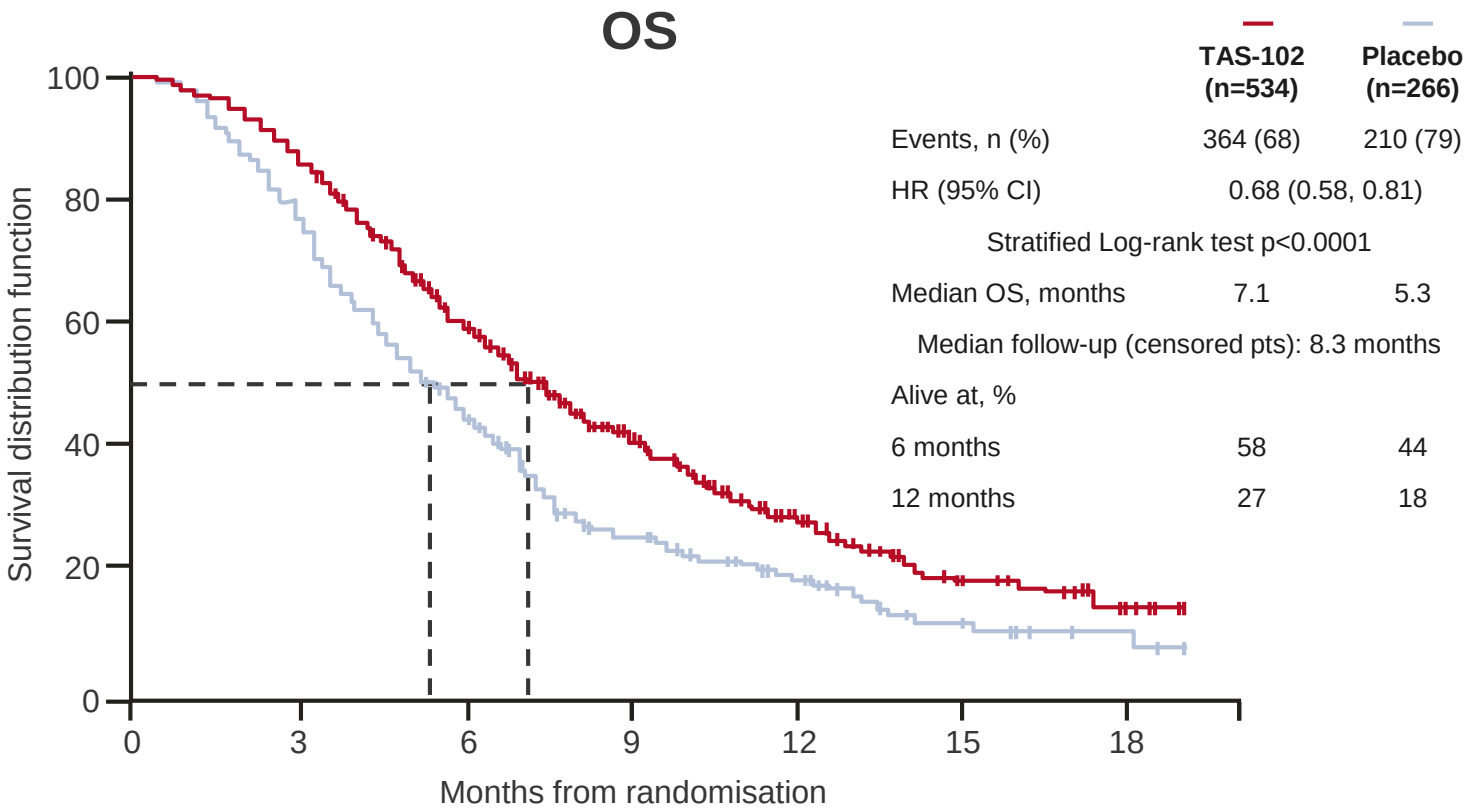
- PFS, safety, tolerability, TTF, ORR, DCR, DoR, subgroup by *KRAS* (OS and PFS)

†35 mg/m$^2$ bid po d1–5, 8–12 q4w

Van Cutsem et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA13

# LBA13: Phase III RECOURSE trial of TAS-102 vs. placebo, with best supportive care (BSC), in patients (pts) with metastatic colorectal cancer (mCRC) refractory to standard therapies – Van Cutsem E et al.

- **Key results**




  - mPFS: 2.0 months TAS-102 vs. 1.7 months placebo
    - HR 0.48 (95% CI 0.41, 0.57); p<0.0001

Van Cutsem et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA13

# LBA13: Phase III RECOURSE trial of TAS-102 vs. placebo, with best supportive care (BSC), in patients (pts) with metastatic colorectal cancer (mCRC) refractory to standard therapies – Van Cutsem E et al.

- **Key results (cont.)**

| Non-haematological AEs occurring in >20% of all grades, % | TAS-102 (N=533) | | | Placebo (N=265) | | |
|---|---|---|---|---|---|---|
| | All grades | Grade 3 | Grade 4 | All grades | Grade 3 | Grade 4 |
| Nausea | 48.4 | 1.9 | 0 | 23.8 | 1.1 | 0 |
| Decreased appetite | 39.0 | 3.6 | 0 | 29.4 | 4.9 | 0 |
| Fatigue | 35.3 | 3.9 | 0 | 23.4 | 5.7 | 0 |
| Diarrhoea | 31.9 | 2.8 | 0.2 | 12.5 | 0.4 | 0 |
| Vomiting | 27.8 | 2.1 | 0 | 14.3 | 0.4 | 0 |

  - Anaemia/neutropenia: 76.5%/66.9% with TAS-102 vs. 33.1%/0.8% with placebo
  - SAEs: 29.6% with TAS-102 vs. 33.6% with placebo
  - Time to ECOG PS ≥2: TAS-102 5.7 months vs. placebo 4.0 months ($p<0.0001$)

- **Conclusions**
  - **Significant improvements in OS and PFS with TAS-102 vs. placebo in patients with mCRC refractory or intolerant to standard therapies**
  - **TAS-102 was well tolerated**
    - **The most frequent toxicities were GI and haematologic**
    - **TAS-102 significantly prolonged the time to EGOG PS ≥2**

Van Cutsem et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA13

# 507PD: POSEIDON Phase I/II trial: Abituzumab combined with cetuximab plus irinotecan as second-line treatment for patients with KRAS wild-type metastatic colorectal cancer – Élez E et al.

- **Study objective**
  - To evaluate prognostic biomarkers in patients with mCRC treated with abituzumab combined with second-line standard of care (SoC)
- **Study design**
  - Immunohistochemistry (n=197) and plasma protein analyses (n=888) were conducted to determine tumour expression of relevant biomarkers
- **Key results**

| Biomarker | Low vs. high expression in SoC arm | | High expression in abituzumab vs. SoC* | |
|---|---|---|---|---|
| | mOS HR (95% CI) | p-value | mOS HR (95% CI) | p-value |
| αvβ6 | 1.96 (1.04, 3.68) | 0.037 | 0.48 (0.28, 0.82) | 0.008 |
| αv | 1.60 (0.83, 3.07) | 0.161 | 0.53 (0.31, 0.92) | 0.025 |
| αvβ5 | 1.44 (0.78, 2.66) | 0.248 | 0.78 (0.46, 1.34) | 0.369 |
| CCL23 | 1.77 (0.97, 3.25) | 0.068 | 0.41 (0.23, 0.75) | 0.0048 |

- **Conclusions**
  - **High αvβ6 + αv expression signified poor prognosis in patients with mCRC**
    - **OS was improved with abituzumab vs. SoC in this population**
  - **CCL23 expression, a ligand for CCR1, was associated with poor prognosis**

*In patients with high biomarker expression

Élez et al. Ann Oncol 2014; 25 (suppl 4): abstr 507PD

# 508PD: 2nd-line therapies after 1st-line therapy with FOLFIRI in combination with cetuximab or bevacizumab in patients with KRAS wild-type metastatic colorectal cancer (mCRC)-analysis of the AIO KRK 0306 (FIRE 3) trial – Modest D et al.

- **Study objective**
  - To investigate how first-line efficacy affects the choice and duration of second-line therapy and how second-line therapy impacts OS in patients with mCRC
- **Study design**
  - Post-hoc analysis of FIRE-3 study; first-line therapy: FOLFIRI + either cetuximab (n=260*) or bevacizumab (n=250*); second-line therapy was physician's choice but protocol recommended FOLFOX + bevacizumab or irinotecan + cetuximab
- **Key results**

| | Second-line monoclonal antibody therapy | | | Second-line oxaliplatin use | |
|---|---|---|---|---|---|
| | Anti-VEGF | Anti-EGFR | No mAB | Oxaliplatin | No oxaliplatin |
| First-line PFS (months) | 9.2 | 9.7 | 11.3 | 9.9 | 9.9 |
| p-value | 0.001 | | | 0.56 | |

  - Second-line therapy duration: 17.2 weeks in patients on first-line cetuximab vs. 14.0 weeks in patients on first-line bevacizumab (p=0.08)
- **Conclusions**
  - **Second-line mAb therapy was favoured in patients with shorter first-line PFS**
  - **Second-line treatment without antibodies was associated with longer OS**

*patients alive after first-line therapy

Modest et al. Ann Oncol 2014; 25 (suppl 4): abstr 508PD

## Poster discussion: Metastatic colorectal cancer (506PD, 507PD, 508PD, 509PD) – Pfeiffer P

- High αv expression defined a group of mCRC patients with poor prognosis
  - Abituzumab combined with cetuximab plus irinotecan improved OS
  - These results should be confirmed in prospective trials
- Primary tumour location was not predictive for benefit of chemotherapy
  - It may be a predictive marker for benefit of EGFR inhibitors and bevacizumab (higher efficacy in left colon)
- Primary tumour location should be reported in ongoing and future trials
  - Preferably exact location
  - Re-biopsy of metastasis or liquid biopsies in clinical trials
- Treatment breaks seem safe, but need to be individualised
  - “Treatment beyond PD” has been accepted by oncologists, not only for bevacizumab but also for 5-FU, irinotecan and EGFR inhibitors
  - It would be interesting if the CALGB investigators did a similar subgroup analysis

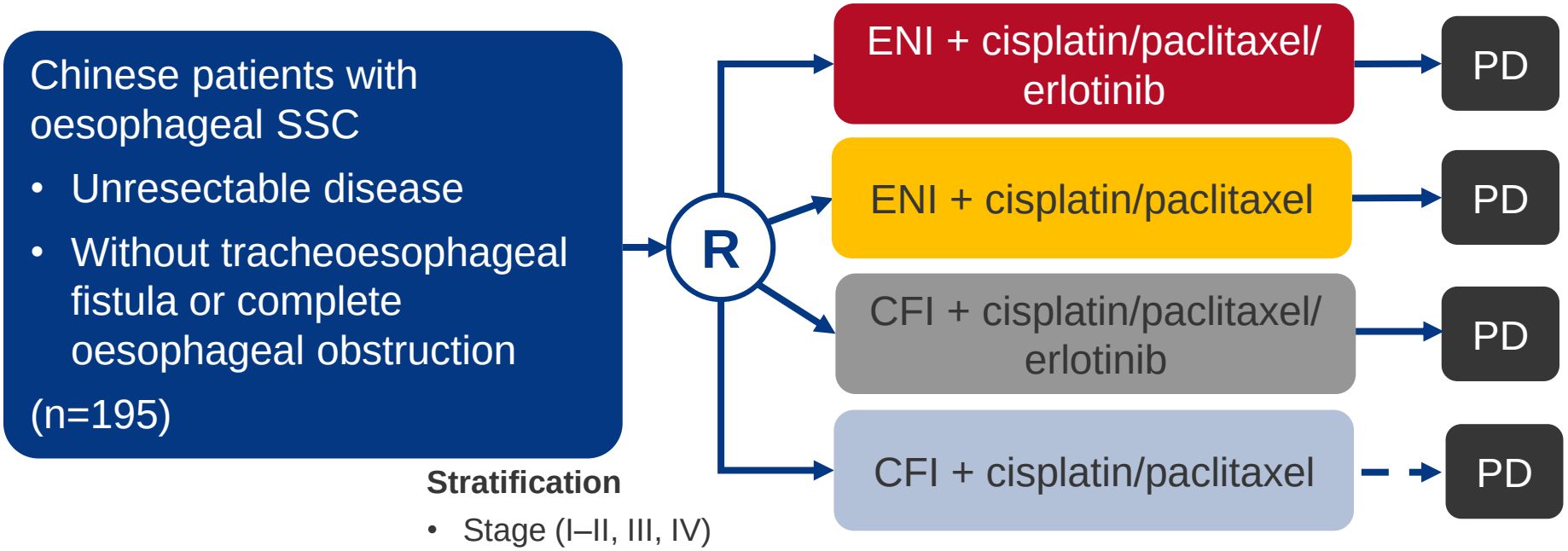
# OESOPHAGEAL AND GASTRIC CANCER

OESOPHAGEAL AND GASTRIC CANCER

# LOCALISED DISEASE

# 619PD: Interim results of a randomized controlled phase III trial of elective nodal irradiation plus erlotinib combined with chemotherapy for esophageal squamous cell carcinoma (NCT00686114) – Wu S et al.

- **Study objective**
  - To determine whether the addition of elective nodal irradiation (ENI) ± erlotinib to concurrent chemoradiotherapy (cisplatin/paclitaxel) improved survival in patients with oesophageal SCC compared with conventional-field irradiation (CFI)




**Stratification**

- Stage (I–II, III, IV)

**Primary endpoint**

- OS

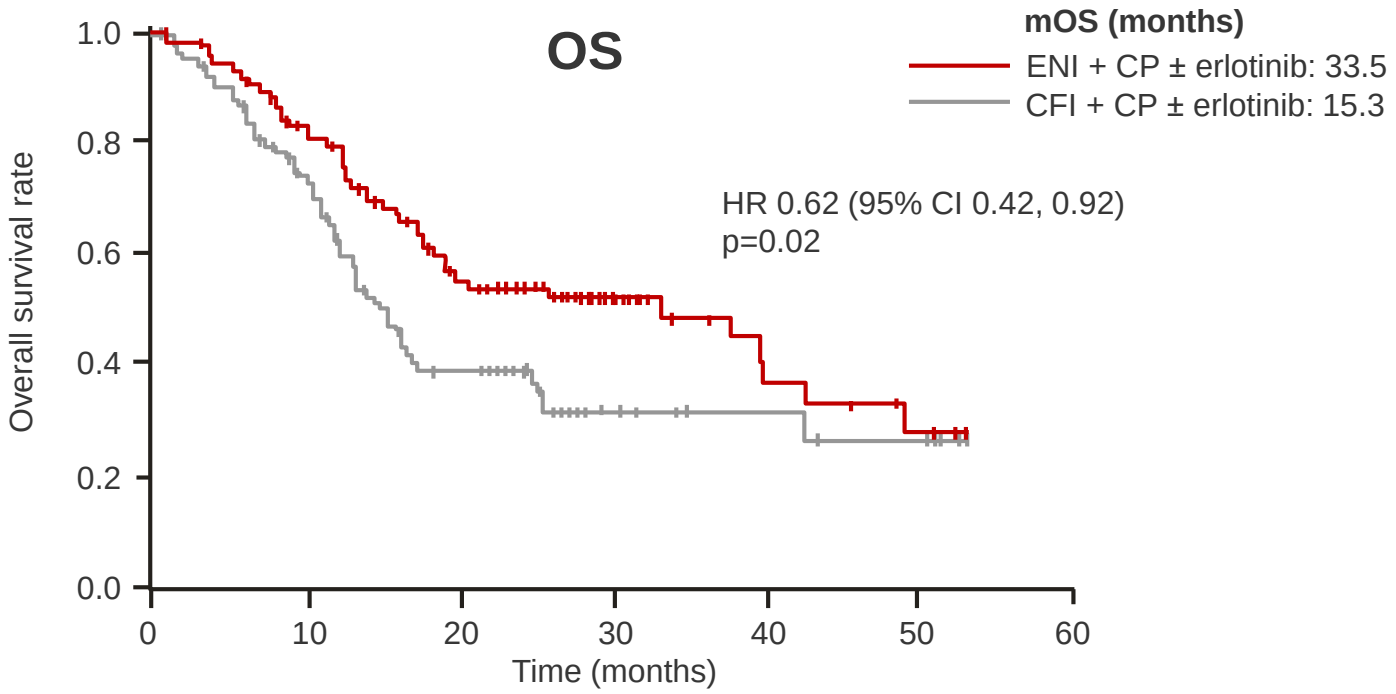
**Secondary endpoints**

- PFS, local-regional failure rate, toxicity

Wu et al. Ann Oncol 2014; 25 (suppl 4): abstr 619PD

# 619PD: Interim Results of a Randomized Controlled Phase III Trial of Elective Nodal Irradiation Plus Erlotinib Combined With Chemotherapy for Esophageal Squamous Cell Carcinoma (NCT00686114) – Wu S et al.

- **Key results**




  - OS for patients treated with ENI + erlotinib: 40.2 months

- **Conclusions**
  - **There was a trend towards improved survival with ENI compared with CFI**
  - **The addition of erlotinib to ENI + cisplatin/paclitaxel further improved OS**

CFI, conventional-field irradiation; CP, cisplatin/paclitaxel;
ENI, elective nodal irradiation

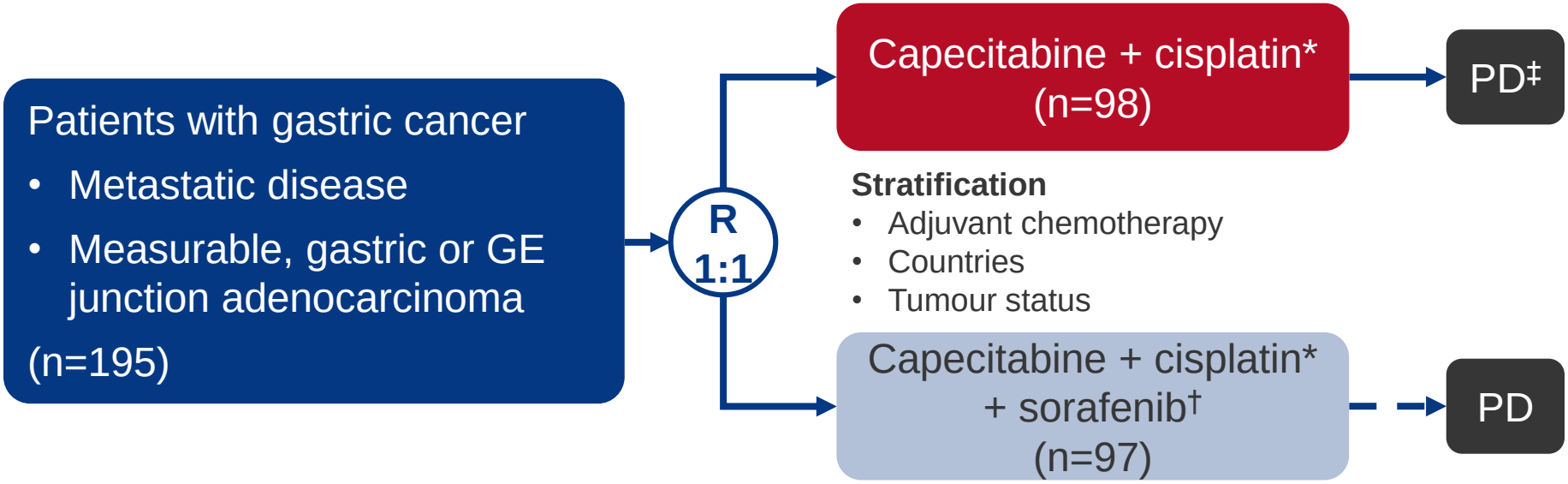
Wu et al. Ann Oncol 2014; 25 (suppl 4): abstr 619PD

OESOPHAGEAL AND GASTRIC CANCER

# METASTATIC DISEASE

# 615O: Randomized phase II study of capecitabine and cisplatin with or without sorafenib in patients with metastatic gastric cancer: STARGATE study – Kang YK et al.

- **Study objective**
  - To evaluate the efficacy and safety of sorafenib in combination with capecitabine + cisplatin in patients with metastatic gastric cancer




**Primary endpoint**

- PFS

**Secondary endpoints**

- OS, RR
- Safety, biomarker analysis

*Capecitabine 1000 mg/m$^2$ po bid d1–14, cisplatin 80 mg/m$^2$ iv d1 (8 cycles);
†400 mg po bid d1–21;
‡Crossover to sorafenib permitted after PD

Kang et al. Ann Oncol 2014; 25 (suppl 4): abstr 615O

# 615O: Randomized phase II study of capecitabine and cisplatin with or without sorafenib in patients with metastatic gastric cancer: STARGATE study – Kang YK et al.

- **Key results**

| | Capecitabine + cisplatin alone | Capecitabine + cisplatin + sorafenib | HR (CI) | p-value |
|---|---|---|---|---|
| PFS, months | 5.3 | 5.6 | 0.92 (0.67, 1.27) | 0.609 |
| OS, months | 10.8 | 11.7 | 0.93 (0.65, 1.31) | 0.661 |
| ORR, % | 51 | 54 | - | 0.826 |

| Biomarkers for sorafenib | HR for PFS (95% CI) |
|---|---|
| Tissue pERK H-score | |
| ≤median (n=86) | 1.29 (0.81, 2.06) |
| >median (n=67) | 0.53 (0.31, 0.91) |
| Tissue VEGF H-score | |
| ≤median (n=76) | 1.41 (0.84, 2.36) |
| >median (n=75) | 0.56 (0.33, 0.93) |

Kang et al. Ann Oncol 2014; 25 (suppl 4): abstr 615O

## 615O: Randomized phase II study of capecitabine and cisplatin with or without sorafenib in patients with metastatic gastric cancer: STARGATE study – Kang YK et al.

- **Key results (cont.)**

| AEs grade ≥3, % | Capecitabine + cisplatin (N=96) | Capecitabine + cisplatin + sorafenib (N=97) | p-value |
|---|---|---|---|
| Leukopenia | 6.3 | 2.1 | 0.144 |
| Neutropenia | 36.5 | 20.6 | **0.015** |
| Anaemia | 13.5 | 10.3 | 0.488 |
| Thrombocytopenia | 5.2 | 8.2 | 0.400 |
| Febrile neutropenia | 6.3 | 2.1 | 0.144 |
| Thromboembolic event | 5.2 | 5.2 | 0.987 |
| Hand-foot syndrome | 1.0 | 7.2 | **0.031** |
| Fatigue | 5.2 | 3.1 | 0.461 |
| Bilirubin increase | 2.1 | 5.2 | 0.254 |
| Anorexia | 5.2 | 0 | **0.023** |

- **Conclusions**
  - **Sorafenib added to capecitabine + cisplatin was tolerated but had a similar efficacy to capecitabine + cisplatin alone**
  - **pERK and VEGF expression levels may have predictive role for determining PFS response**

Kang et al. Ann Oncol 2014; 25 (suppl 4; abstr 615O)

# 620PD: Proton pump inhibitor (PPIs) therapy may impair capecitabine (cape) efficacy in metastatic gastroesophageal cancer (GEC), results from the TRIO-013/LOGIC trial – Chu M et al.

- **Study objective**
  - A post-hoc analysis to assess the impact of proton pump inhibitors (PPIs) in patients with HER2+ metastatic gastroesophageal cancer (GEC) receiving capecitabine + oxaliplatin with either lapatinib or placebo
- **Study design**
  - 545 patients were randomised 1:1 to capecitabine + oxaliplatin with either lapatinib or placebo and 299 in each arm received PPIs
- **Key results**

| | Capecitabine + oxaliplatin + placebo | | Capecitabine + oxaliplatin + lapatinib | |
|---|---|---|---|---|
| **PPI vs. no PPI** | **Overall analysis** | **Multivariate analysis*** | **Overall analysis** | **Multivariate analysis*** |
| mPFS, HR (95%CI)<br>p-value | 1.55 (1.29,1.81)<br>0.0008 | 1.64 (1.38, 1.90)<br>p=0.0002 | 1.08<br>0.54 | n/a |
| OS, HR (95%CI)<br>p-value | 1.34 (1.04, 1.64)<br>0.04 | 1.39 (1.09, 1.69)<br>p=0.03 | 1.26<br>0.10 | 1.36 (1.06, 1.66)<br>0.03 |

  - Capecitabine + oxaliplatin toxicity was lower than expected given the high dose of capecitabine that was maintained in both arms
- **Conclusion**
  - **PPIs negatively impacted capecitabine efficacy; given the concurrent use of capecitabine it was unclear whether PPIs also affected lapatinib**

*Based on age, race, stage and gender

Chu et al. Ann Oncol 2014; 25 (suppl 4): abstr 620PD

OESOPHAGEAL AND GASTRIC CANCER

# ADVANCED DISEASE

## LBA15: A phase Ib study of pembrolizumab (Pembro; MK-3475) in patients (pts) with advanced gastric cancer – Muro K et al.

- **Study objective**
  - To evaluate the efficacy and safety of pembrolizumab (designed to inhibit PD-1 binding to its ligands PD-L1+2) in patients with advanced gastric cancer
- **Study design**
  - PD-L1 expression was assessed in tumour samples from patients with recurrent/metastatic gastric cancer or GEJ treated with pembrolizumab* (n=39†)
- **Key results**
  - Patients with ≥2 prior therapies: 79% in Asia Pacific vs. 55% in rest of world
  - ORR (confirmed + unconfirmed): 32% in Asia Pacific vs. 30% in rest of world
  - PD-L1 expression appeared to correlate with PFS (p=0.032) and ORR (p=0.071)
  - Most common AEs: hypothyroidism (n=5 [12.8%]) and fatigue (n=5 [12.8%])
- **Conclusions**
  - **Pembrolizumab had anti-tumour activity and was generally well tolerated**
  - **This study supports the further development of pembrolizumab in patients with advanced gastric cancer**

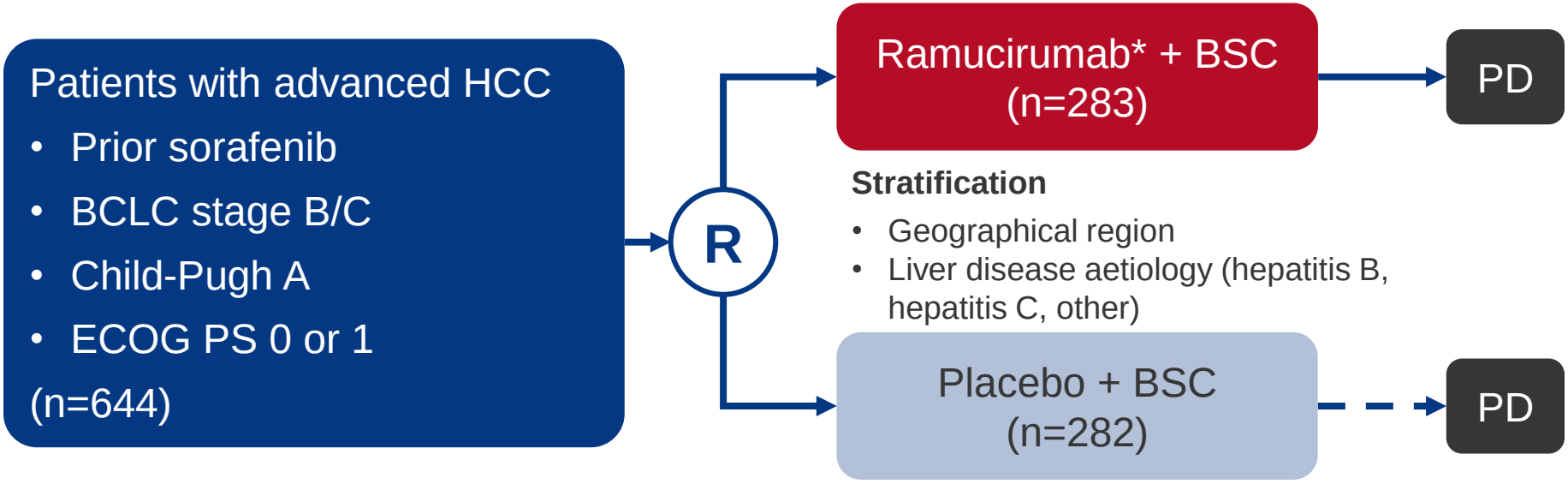
*10 mg/kg q2w ≤24 months; †n=19 in Asia Pacific, n=20 in rest of world

Muro et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA15

# HEPATOCELLULAR CARCINOMA

# LBA16: Ramucirumab (RAM) as second-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC) following first-line therapy with sorafenib: Results from the randomized phase III REACH study – Zhu A et al.

- **Study objective**
  - To assess the efficacy and safety of ramucirumab after first-line treatment with sorafenib in patients with advanced HCC




**Primary endpoint**

- OS

**Secondary endpoints**

- PFS, TTP, ORR
- Safety, patient-reported outcomes

*8mg/kg, q2w per cycle

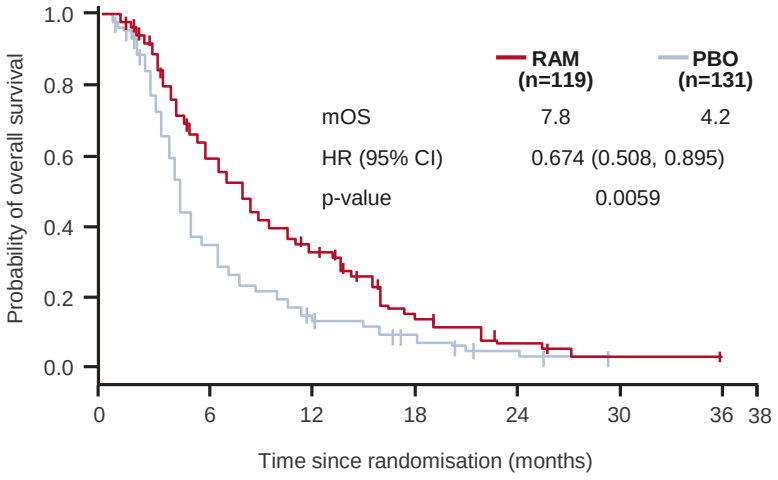
Zhu et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA16

# LBA16: Ramucirumab (RAM) as second-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC) following first-line therapy with sorafenib: Results from the randomized phase III REACH study – Zhu A et al.

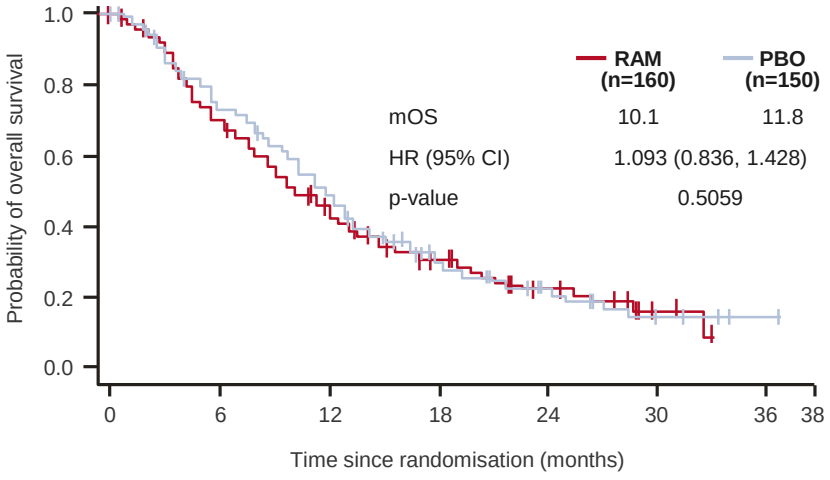
- **Key results**

| | Ramucirumab | Placebo | HR (95% CI) | p-value |
|---|---|---|---|---|
| mOS, months | 9.2 | 7.6 | 0.866 (0.717, 1.046) | 0.1391 |
| mPFS, months | 2.8 | 2.1 | 0.625 (0.522, 0.750) | <0.0001 |
| mTTP, months | 3.5 | 2.6 | 0.593 (0.487, 0.722) | <0.0001 |
| ORR, n (%) | 20 (7.1) | 2 (0.7) | - | <0.0001 |
| DCR, n (%) | 159 (56.2) | 129 (45.7) | - | 0.0110 |

AFP ≥400 ng/mL




AFP <400 ng/mL




AFP, alpha-fetoprotein

Zhu et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA16

# LBA16: Ramucirumab (RAM) as second-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC) following first-line therapy with sorafenib: Results from the randomized phase III REACH study – Zhu A et al.

- **Key results (cont.)**

| AE of special interest, n (%) | Ramucirumab (N=277) | | Placebo (N=276) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Liver injury/failure | 140 (51)* | 58 (21) | 103 (37) | 65 (24) |
| Bleeding/haemorrhage | 90 (33)* | 17 (6) | 55 (20) | 21 (8) |
| Hypertension | 56 (20)* | 35 (13)* | 20 (7) | 10 (4) |
| Proteinuria | 48 (17)* | 6 (2)* | 13 (5) | 0 |
| Renal failure | 20 (7) | 6 (2) | 18 (7) | 3 (1) |
| Infusion-related reaction | 20 (7)* | 3 (1) | 2 (<1) | 0 |

- **Conclusions**
  - **Ramucirumab did not significantly improve OS compared with placebo in patients with advanced HCC**
  - **Ramucirumab was associated with clinically meaningful differences in PFS, TTP and ORR vs. placebo**
  - **Patients with elevated baseline AFP levels may benefit from ramucirumab**
  - **Ramucirumab had an acceptable safety profile**

*p<0.05 for ramucirumab vs. placebo

Zhu et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA16

# LBA17: Randomised study of axitinib (Axi) plus best supportive care (BSC) versus placebo (Pbo) plus BSC in patients with advanced hepatocellular carcinoma (HCC) following prior antiangiogenic therapy – Kang Y et al.

- **Study objective**
  - To assess the VEGFR inhibitor axitinib + best supportive care (BSC) vs. placebo + BSC in patients with locally advanced or metastatic HCC
- **Study design**
  - Patients who had failed one prior antiangiogenic therapy with ECOG PS 0–1 were randomised to axitinib + BSC (n=134) vs. placebo + BSC (n=68)
- **Key results**

| | Axitinib + BSC | Placebo + BSC | HR (95% CI) | p-value |
|---|---|---|---|---|
| mOS, months | 12.7 | 9.7 | 0.87 (0.62, 1.22) | 0.211 |
| mPFS, months | 3.6 | 1.9 | 0.62 (0.44, 0.87) | 0.004 |
| ORR, % | 9.7 | 2.9 | - | 0.083 |

  - Most common AEs occurring in >40% in either group (axitinib vs. placebo): diarrhoea (54% vs. 12%), hypertension (54% vs. 13%) and decreased appetite (47% vs. 21%)
- **Conclusion**
  - **Axitinib did not significantly improve mOS but improved mPFS vs. placebo in patients with advanced HCC who received prior antiangiogenic therapy**

Kang et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA17

# PANCREATIC CANCER

PANCREATIC CANCER

# ADJUVANT THERAPY

## LBA18: CONKO-006: A randomized double-blinded phase IIb-study of adjuvant therapy with gemcitabine + sorafenib/placebo for patients with R1-resection of pancreatic cancer – Sinn M et al.

- **Study objective**
  - To evaluate the efficacy and safety of gemcitabine with either sorafenib or placebo following R1 resection in patients with pancreatic cancer
- **Study design**
  - Patients with R1-resected pancreatic cancer were randomised to gemcitabine* + sorafenib† (Arm 1; n=57) or gemcitabine* + placebo (Arm 2; n=65) for 12 cycles
- **Key results**
  - mDFS Arm 1 vs. Arm 2: 9.6 vs. 10.7 months; p=0.89
  - OS Arm 1 vs. Arm 2: 17.6 vs. 15.6 months; p=0.90
  - Median treatment duration: 27 weeks in Arm 1 vs. 27 weeks in Arm 2
  - Grade 3/4 toxicities (Arm 1 vs. Arm 2): diarrhoea (6% vs. 1%), fatigue (2% vs. 0%), neutropenia (7% vs. 16%), thrombocytopenia (4% vs. 1%), elevated GGT (8% vs. 5%), hypertension (2% vs. 0%) and hand-foot syndrome (3% vs. 0%)
- **Conclusion**
  - **The addition of sorafenib to gemcitabine did not improve DFS or OS vs. gemcitabine alone in this high-risk cancer cohort**

*1000 mg/m$^2$ iv d1,8,15, q29d; †200 mg po bid, d1–28, q29d

Sinn et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA18

PANCREATIC CANCER

# FIRST-LINE THERAPY

## 616PD: A ph 1b study of the anti-cancer stem cell agent demcizumab (DEM) & gemcitabine (GEM) +/- paclitaxel protein bound particles (nab-paclitaxel) in pts with pancreatic cancer – Hidalgo M et al.

- **Study objective**
  - To assess the efficacy and safety of demcizumab (an anti-delta-like ligand 4 [DLL4] antibody) as first-line in patients with pancreatic cancer
- **Study design**
  - Open-label dose escalation trial; 47 patients received demcizumab* + gemcitabine† (Arm 1) or demcizumab* + gemcitabine† + nab-paclitaxel‡ (Arm 2)
- **Key results**
  - Most common AEs occurring in >60% in either group (Arm 1/2): fatigue 63%/74%, nausea 63%/61%, vomiting 63%/57%, diarrhoea 38%/70%
  - Grade 2 pulmonary hypertension and heart failure occurred in 1 patient
  - Response (Arm 1/2): PR 25%/41%, SD 44%/45%, PR+SD 69%/86%, PD 31%/14%
  - mPFS for demcizumab: 2.5 mg/kg + nab-paclitaxel: 9.1 months; 5 mg/kg q4w: 7 months; 2.5 mg/kg q4w: 1.7 months; 2.5 mg/kg q2w: 3.4 months
- **Conclusions**
  - **Treatments were generally well tolerated in patients with pancreatic cancer**
  - **Concomitant gemcitabine ± nab-paclitaxel did not appear to significantly alter the pharmacokinetics of demcizumab**

*2.5 or 5 mg/kg q2w or q4w, or 3.5 mg/kg q2w;
†1000 mg/m$^2$ 7 of 8 wks, then 3 of 4 wks; ‡125 mg/m$^2$ d0, 7, 14 q4w

Hidalgo et al. Ann Oncol 2014; 25 (suppl 4): abstr 616PD

## 617PD: A phase III trial comparing FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer – Singhal M et al.

- **Study objective**
  - To the assess efficacy and safety of FOLFIRINOX vs. gemcitabine as first-line therapy in patients with metastatic pancreatic cancer
- **Study design**
  - Patients (n=310; ECOG PS 0–1) were randomised to either FOLFIRINOX* or gemcitabine†
- **Key results**

| | FOLFIRINOX | Gemcitabine | HR (95% CI) | p-value |
|---|---|---|---|---|
| mOS, months | 10.8 | 7.4 | 0.48 (0.41, 0.68) | <0.001 |
| mPFS, months | 5.6 | 3.1 | 0.44 (0.29, 0.49) | <0.001 |
| ORR, % | 29.6 | 8.3 | - | <0.001 |
| Degradation in QoL at 6 months, % | 29 | 59 | 0.45 (0.29, 0.68) | <0.001 |

  - More AEs were reported in the FOLFIRINOX group
- **Conclusion**
  - **FOLFIRINOX is a treatment option for patients with metastatic pancreatic cancer with good performance status**

*Oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m², fluorouracil 400 mg/m² bolus then 2,400 mg/m² 46-h continuous infusion q2w; †1000 mg/m² d1, 8, 15 (28-d cycle) for 6 cycles

Singhal et al. Ann Oncol 2014; 25 (suppl 4): abstr 617PD

## 618PD: A phase 2 randomized, double-blind, placebo controlled study of simtuzumab or placebo in combination with gemcitabine for the first line treatment of pancreatic adenocarcinoma – Benson A et al.

- **Study objective**
  - To evaluate simtuzumab therapy in patients with metastatic pancreatic cancer
- **Study design**
  - Patients with metastatic pancreatic cancer (n=234; ECOG PS 0–1) were randomised to gemcitabine* plus either simtuzumab† or placebo until PD
- **Key results**

| | SIM 700 mg vs. placebo | | SIM 200 mg vs. placebo | | SIM 700 mg vs. SIM 200 mg | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| mPFS | 1.08 (0.73, 1.60) | 0.746 | 1.12 (0.76, 1.66) | 0.628 | 0.96 (0.64, 1.44) | 0.982 |
| ORR | –0.09 (–0.21, 0.03) | 0.159 | –0.08 (–0.21, 0.02) | 0.201 | –0.002 (–0.11, 0.11) | 0.977 |
| mOS | 0.83 (0.56, 1.22) | 0.259 | 1.05 (0.72, 1.53) | 0.762 | 0.79 (0.54, 1.16) | 0.246 |

  - AEs grade ≥3: simtuzumab 700 mg 67.1%, simtuzumab 200 mg 63.2% and placebo 70.4%
- **Conclusion**
  - **Simtuzumab added to gemcitabine did not improve PFS, OS or ORR vs. placebo in patients with advanced pancreatic cancer**

*iv d1, 8, 15; †200 mg or 700 mg d1, 8 15

Benson et al. Ann Oncol 2014; 25 (suppl 4): abstr 618PD

# LBA19: A multi-institutional randomized phase 2 trial of the oncolytic virus reolysin in the first line treatment metastatic adenocarcinoma of the pancreas (MAP) – Bekaii-Saab T et al.

- **Study objective**
  - To examine whether the addition of reolysin (a proprietary form of reovirus, a naturally occurring virus that mediates tumour cell oncolysis) to paclitaxel + carboplatin improves survival in patients with metastatic pancreatic cancer
- **Study design**
  - Patients were randomised to paclitaxel* + carboplatin‡ (n=36) or paclitaxel* + carboplatin‡ + reolysin† (n=37); *KRAS* status was assessed (n=60)
- **Key results**

| | Paclitaxel + carboplatin | Paclitaxel + carboplatin + reolysin | p-value |
|---|---|---|---|
| mPFS, months | 4.9 | 5.2 | 0.87 |
| mOS, months | 7.1 | 8.9 | 0.24 |
| PR/SD/PD/NE, % | 7/19/8/2 | 7/16/13/1 | 0.62 |
| ≥75% reduction in CA19-9, n | 5 | 11 | 0.09 |

  - mPFS by *KRAS* status (n=60): wt 5.6 months vs. mutant 4.9 months; p=0.64
- **Conclusions**
  - **Addition of reolysin to paclitaxel + carboplatin did not improve outcome, regardless of *KRAS* status**
  - **Paclitaxel + carboplatin has not been assessed in metastatic pancreatic cancer before and had a higher activity than expected**

*175 mg/m$^2$ iv; †AUC 5 iv; ‡3x10$^{10}$ $TCID_{50}$ /day iv d1–5 q3w

Bekaii-Saab et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA19

## Poster discussion: Advanced pancreatic cancer (616PD, 617PD, 618PD, LBA19) – Valle JW

- Pancreatic cancer is predicted to become the second leading cause of cancer death by 2020, underscoring the need for new therapies
- Curative treatment options for advanced disease include gemcitabine, gemcitabine + nab-paclitaxel or FOLFIRINOX
- FOLFIRINOX treatment (617PD)
  - Significantly improved ORR, increased toxicity, reduced degradation in QoL
  - Limitations: no detailed toxicity data; QoL tool not defined; no demographic data for context
- Oncolytic virus therapy (LBA19)
  - Results do not warrant further study as they currently stand
  - Is duration of treatment too short? Is it too late in time-course of disease?
- Lysyl oxidase – simtuzumab therapy (618PD)
  - Would nab-paclitaxel have been a more appropriate agent than gemcitabine?
- Targeting Notch – demcizumab (616PD)
  - Cardiac toxicity appears manageable
  - May not be effective if Notch receptor genes are overactive
  - Will the cancer stem cell approach succeed where VEGF inhibition has failed?

# BILIARY TRACT CANCER

# 622PD: Does the derived neutrophil lymphocyte ratio predict benefit from cisplatin and gemcitabine compared with gemcitabine alone in advanced biliary cancer? An exploratory study of the ABC-02 trial – Grenader T et al.

- **Study objective**
  - To assess the prognostic value of dNLR in patients with advanced biliary cancer
- **Study design**
  - A post-hoc analysis of the ABC-02 trial on all patients with white blood cell and absolute neutrophil count data
  - Patients received cisplatin + gemcitabine (n=160) vs. gemcitabine alone (n=162)
- **Key results**
  - OS overall population: HR (dNLR <3 vs. ≥3): 1.87 (95% CI 1.44, 2.44); p<0.001

| OS | Cisplatin + gemcitabine vs. Gemcitabine alone |
|---|---|
| dNLR <3 | HR 0.51 (95% CI 0.39, 0.69); p<0.001 |
| dNLR ≥3 | HR 0.95 (95% CI 0.62, 1.46); p=0.83 |

  - Long-term survivors (>24 months): 19.8% for dNLR <3 and 4.3% for dNLR ≥3 with cisplatin + gemcitabine compared with 5.7% for dNLR <3 and 5.4% for dNLR ≥3 with gemcitabine alone
- **Conclusion**
  - **dNLR <3 indicated better survival in patients with advanced biliary cancer and may be predictive of benefit of cisplatin + gemcitabine vs. gemcitabine alone**

dNLR, derived neutrophil to lymphocyte ratio

Grenader et al. Ann Oncol 2014; 25 (suppl 4): abstr 622PD

# NEUROENDOCRINE TUMOURS

NEUROENDOCRINE TUMOURS

# PROGNOSIS / BIOMARKERS

## 1133O: Molecular profiling of small intestinal neuroendocrine tumours – Karpathakis A et al.

- **Study objective**
  - To investigate the molecular profiles of small intestinal NETs in order to identify key differentially expressed genes that may contribute to tumourigenesis

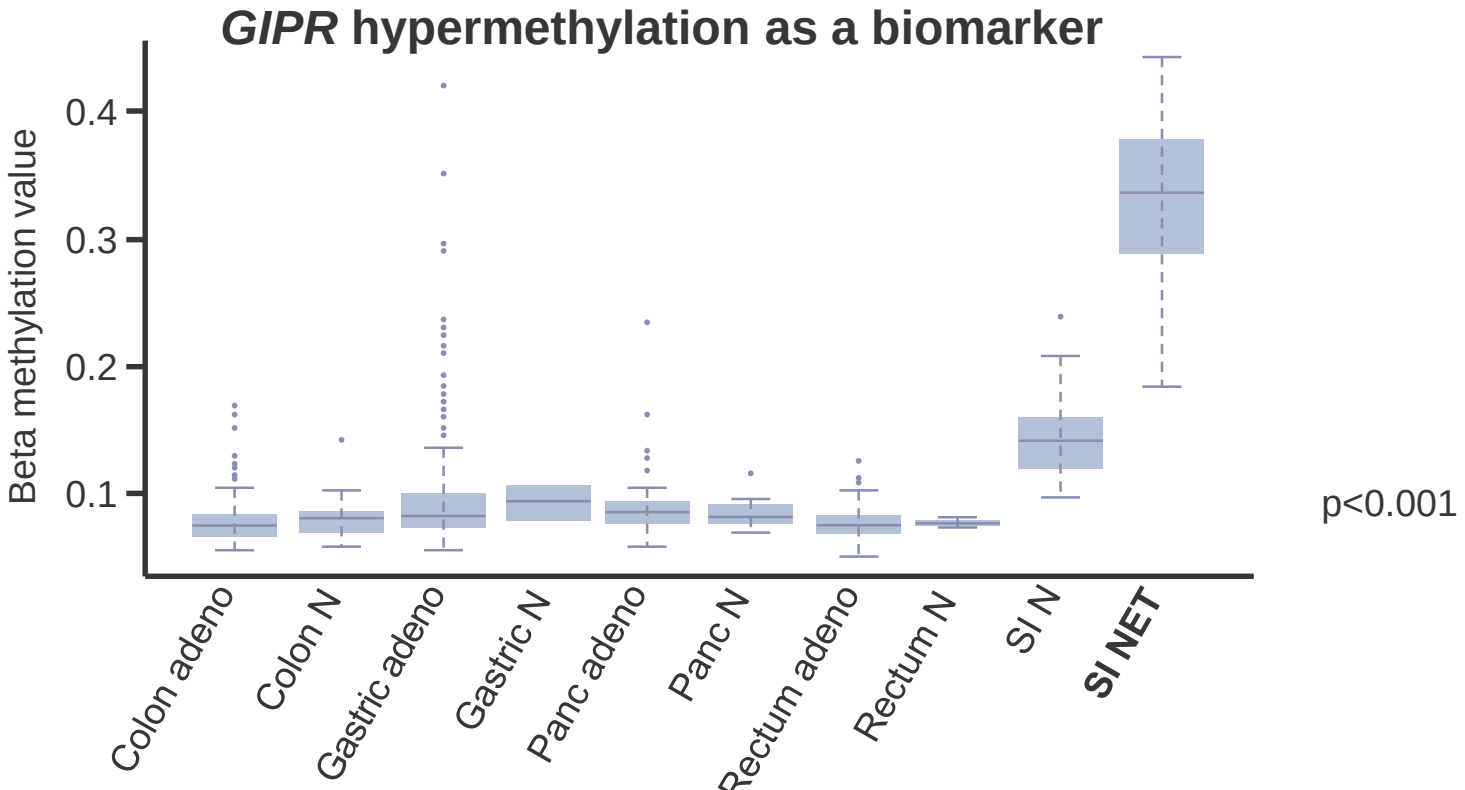
- **Study design**
  - 49 samples from patients with small intestinal NETs vs. 21 matched normal small intestinal samples were analysed
  - DNA methylation was assessed using the HumanMethylation450 BeadChip
    - 130,083 MVPs were identified (7,354 with >30% differential methylation)
  - RNA expression was assessed using the Whole Genome DASL HT assay
    - 2,415 signature probes were identified (733 with >3x fold change)

MVP, methylation variable position

Karpathakis et al. Ann Oncol 2014; 25 (suppl 4): abstr 1133O

## 1133O: Molecular profiling of small intestinal neuroendocrine tumours – Karpathakis A et al.

- **Key results**
  - A signature of 11 epimutated genes was identified:
    - Down-regulation of *CDX1, FBP1, C20orf54, GATA5*
    - Up-regulation of *PTPRN, PCSK1, PRLHR, CELSR3, GIPR, LMX1B, SCGN*




Adeno, adenocarcinoma; N, normal; panc, pancreas; SI, small intestine

Karpathakis et al. Ann Oncol 2014; 25 (suppl 4; abstr 1133O)

## 1133O: Molecular profiling of small intestinal neuroendocrine tumours – Karpathakis A et al.

- **Key results (cont.)**
  - Aberrant *GIPR* methylation correlated with increased expression
    - 76% of NET samples were >30% differentially methylated vs. normal samples
    - 84% of NET samples had >3-folder greater expression vs. normal samples
    - Expression in liver metastases vs. normal small intestine: $p<0.001$
    - Expression in small intestine NET (primary) vs. normal small intestine: $p<0.001$
    - Expression in liver metastases vs. small intestine NET (primary): $p=0.27$

- **Conclusions**
  - **This is the first genome-wide molecular profile study of small intestinal NETs**
  - **An 11 gene panel that showed differential methylation and expression in small intestine NETs was identified**
  - ***GIPR* is a promising biomarker for the detection of small intestine NETs**

Karpathakis et al. Ann Oncol 2014; 25 (suppl 4): abstr 1133O

# 1140PD: Finding molecular subgroups of worse prognosis studying the microenvironment of gastro-entero-pancreatic neuroendocrine tumours (GEP-NET) – Barriuso J et al.

- **Study objective**
  - To establish a link between the expression of tumour suppressor gene protein products and proteins in the microenvironment of GEP-NETs
- **Study design**
  - Using tissue microarray construction and immunohistochemistry, protein products (p27 and PTEN) from tumour suppressor genes CDKN1B and PTEN were examined in FFPEs from patients who underwent surgery for GEP-NET
- **Key results**
  - Both p27 and PTEN were independent prognostic factor for DFS when adjusted by grade and stage (p=0.023 and p=0.028, respectively)
    - Within the PTEN− subgroup, LOXL2+ conferred protection for DFS (p<0.001), multivariate survival analysis HR 0.15 (95% CI 0.29, 8.25)
    - β-catenin nuclear expression (BCATn) was a negative prognostic factor (p=0.043)
  - In p27− cases, LOXL2+ had longer DFS (p=0.01); multivariate survival analysis HR 0.25 (95% CI 0.08, 0.83)
- **Conclusions**
  - **In patients with GEP-NET, prognosis was worst with p27– LOXL2– or PTEN– LOXL2– tumours**

Barriuso et al. Ann Oncol 2014; 25 (suppl 4): abstr 1140PD

## 1141PD: Gastroenteropancreatic Neuroendocrine Tumors (GEPNET) Registry: Update from an international collaboration – Yalçın Ş et al.

- **Study objective**
  - To assess incidence and prevalence, as well as trends in the diagnosis, management and outcomes of GEP-NET
- **Study design**
  - Longitudinal observational study combining retrospective data collection and prospective follow-up (5 years) of patients with GEP-NET in Israel, Turkey and South Africa and the Asia Pacific, Middle East and North Africa regions
- **Key results**
  - Interim results: of 1,005 patients enrolled, 933 were evaluable (51% female, mean age 54 years, 55% Caucasian)
  - At diagnosis 78% were symptomatic (54% reported one symptom; 27% reported two)
  - Pathology review of tissue was the most common method of diagnosis (99%)
  - The pancreas was the most common primary site (42%), followed by stomach (17%) and other (13%)
  - 97% of patients received ≥1 initial treatment; the most common initial treatment was surgery (61%), followed by somatostatin analogues (17%), then chemotherapy (15%)
  - Median PFS was 57.3 months (95% CI 52.2, 64.4)
- **Conclusion**
  - **Improvements in clinical practice are still needed in the management of GEP-NET**

Yalçın et al. Ann Oncol 2014; 25 (suppl 4): abstr 1141PD

## 1142PD: Large cell neuroendocrine carcinomas (LCNEC) of the lung: Pathologic features, treatment and outcomes – Naidoo J et al.

- **Study objective**
  - To describe features of patients with stage IV large cell neuroendocrine carcinomas (LCNECs) and response to therapy
- **Study design**
  - Data from the Memorial Sloan Kettering Cancer Center (MSKCC) database were retrospectively analysed for patients with stage IV LCNECs between 2006 and 2013
- **Key results**
  - Of 49 identified patients, 33 underwent central pathology re-review
  - *KRAS* mutations were present in 24%; no EGFR mutations or ALK rearrangements were identified
  - No clinical characteristics were significant factors for OS
  - The ORR among 40 treated patients was 36% (95% CI 18, 57), for Plt/E 40% (95% CI 19, 64) and for other regimens 20% (95% CI 0.5, 72)
- **Conclusions**
  - **In patients with LCNECs, ORR and OS are poor, with short time to relapse**
  - **Recurrent LCNEC had a more favourable disease course than de novo disease**
  - **In patients with recurrent LCNEC, improved OS was observed with stage II/III/ oligometastatic disease and adjuvant chemotherapy**

Plt/E, adjuvant or palliative platinum/etoposide doublet chemotherapy

Naidoo et al. Ann Oncol 2014; 25 (suppl 4): abstr 1142PD

## Poster discussion (1140PD, 1141PD, 1142PD) – Ruszniewski P

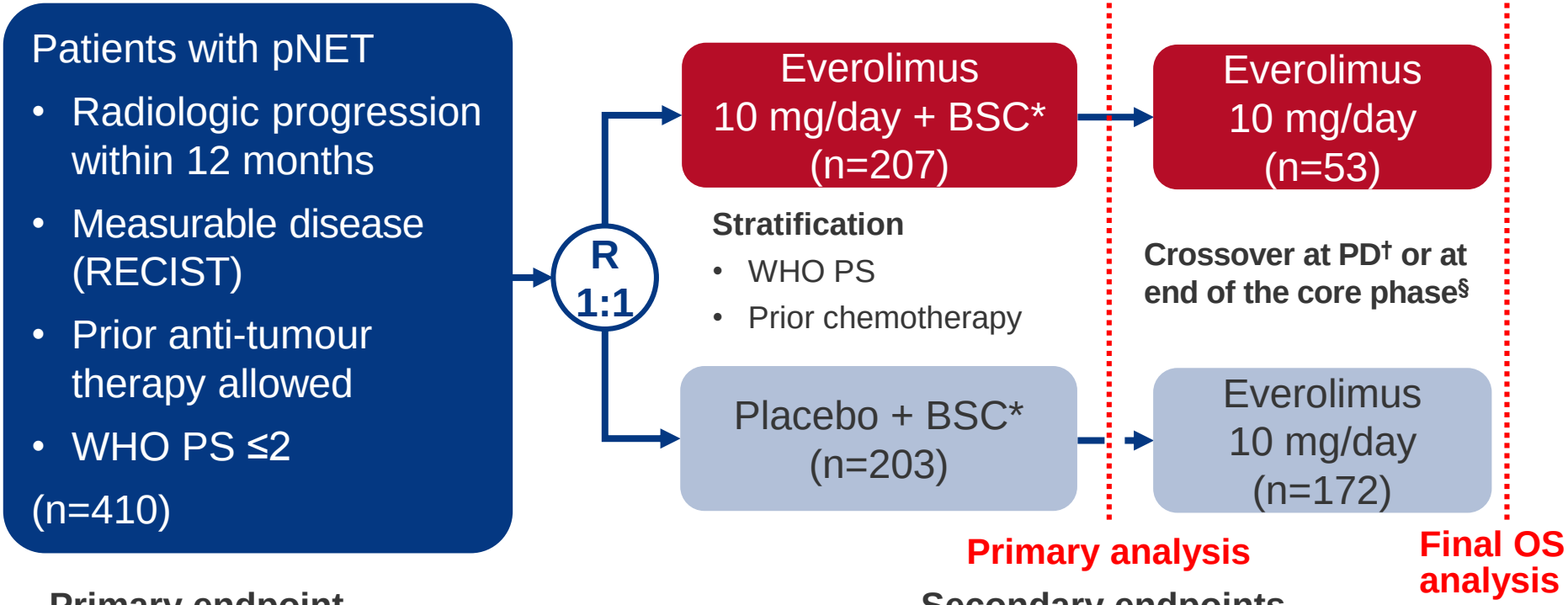
- The GEP-NET registry highlights the need for clinical practice involvement (1140PD)
  - Patients with p27– LOXL2– or PTEN– LOXL2– tumours had worse prognosis
  - These findings warrant further *in-vitro* mechanistic experiments to clarify the relevance of the microenvironment of these diseases
  - Prospective validation studies are also needed to test their prognostic value

NEUROENDOCRINE TUMOURS

# PALLIATIVE

# 1132O: Everolimus (EVE) for the treatment of advanced pancreatic neuroendocrine tumors (pNET): Final overall survival (OS) results of a randomized, double-blind, placebo (PBO)-controlled, multicenter phase III trial (RADIANT-3) – Yao JC et al.

- **Study objective**
  - To assess everolimus vs. placebo treatment in patients with pNET




**Primary endpoint**

- PFS

**Secondary endpoints**

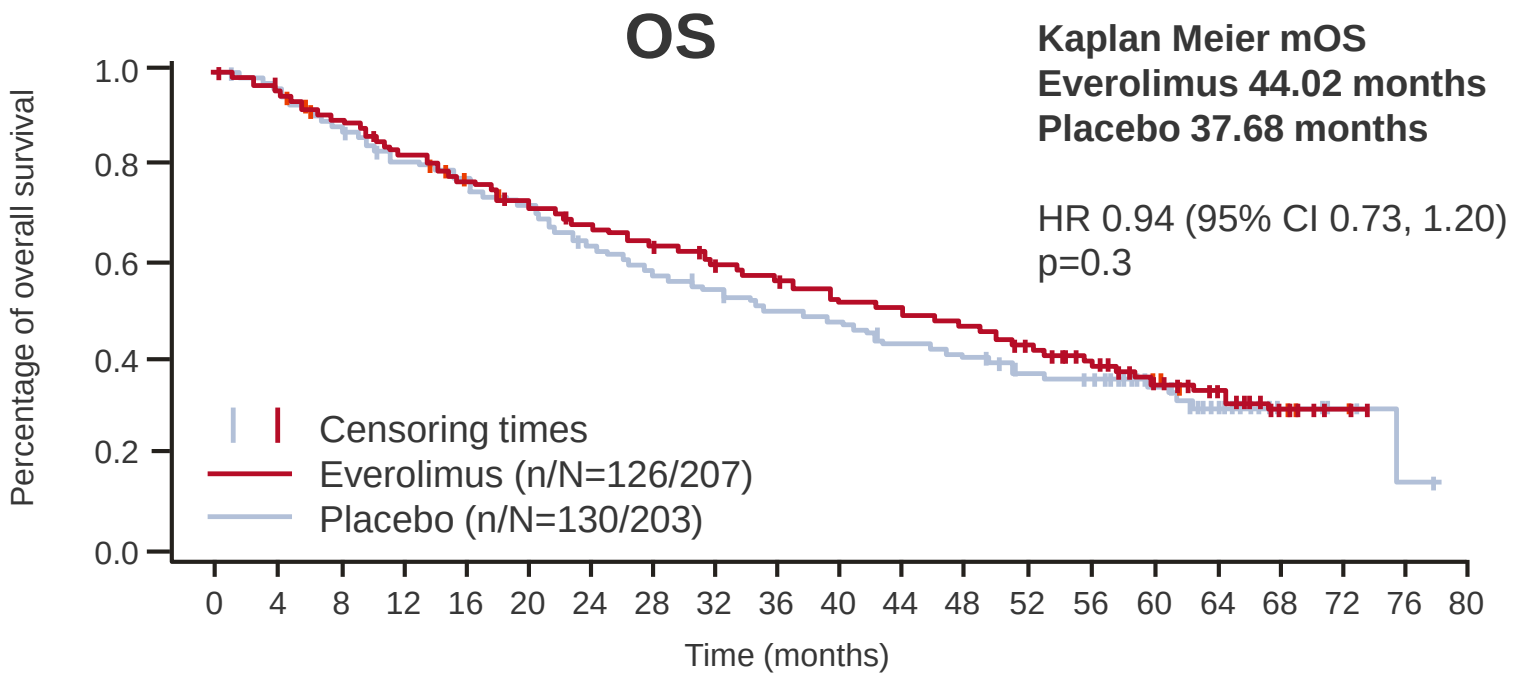
- OS

*Concurrent somatostatin analogues were permitted; †In the core phase, patients randomised to placebo were allowed to crossover to open-label everolimus at PD; §After the core phase, all patients were switched to open-label everolimus

Yao et al. Ann Oncol 2014; 25 (suppl 4): abstr 1132O

# 1132O: Everolimus (EVE) for the Treatment of Advanced Pancreatic Neuroendocrine Tumors (pNET): Final Overall Survival (OS) Results of a Randomized, Double-blind, Placebo (PBO)-Controlled, Multicenter Phase III Trial (RADIANT-3) – Yao JC et al.

- **Key results**
  - PFS: Everolimus 11.04 months vs. placebo 4.60 months
    - HR 0.35 (95% CI 0.27, 0.45); p<0.0001



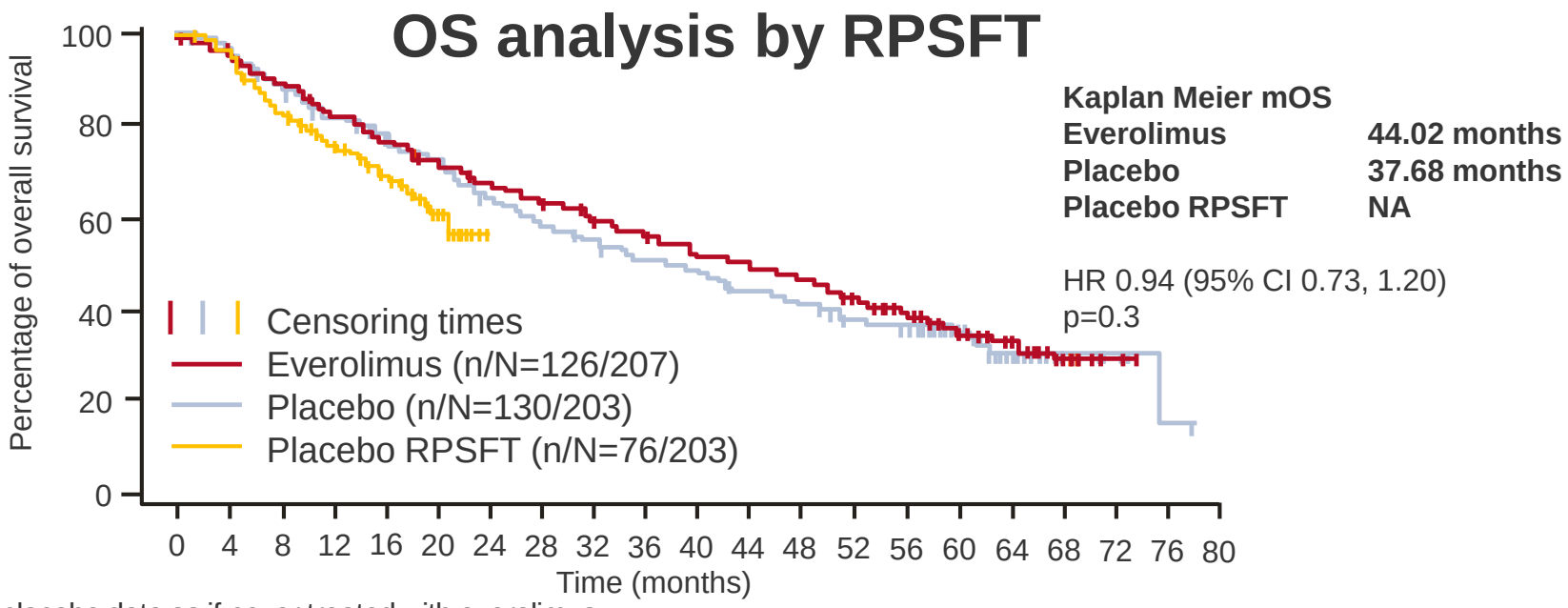

  - 172/203 (85%) of placebo patients crossed over to open-label everolimus

Yao et al. Ann Oncol 2014; 25 (suppl 4): abstr 1132O

# 1132O: Everolimus (EVE) for the Treatment of Advanced Pancreatic Neuroendocrine Tumors (pNET): Final Overall Survival (OS) Results of a Randomized, Double-blind, Placebo (PBO)-Controlled, Multicenter Phase III Trial (RADIANT-3) – Yao JC et al.

- **Key results (cont.)**

| OS KM estimate (95% CI) | Everolimus + BSC (n=207) | Placebo + BSC (n=203) | Placebo corrected by RPSFT* |
|---|---|---|---|
| **Analysis by KM method** | | | |
| 12 months | 82.6 (76.6, 87.2) | 82.0 (75.9, 86.7) | n/a |
| 24 months | 67.7 (60.7, 73.8) | 64.0 (56.8, 70.2) | n/a |
| **Analysis by RPSFT** | | | |
| 12 months | 82.6 (76.6, 87.2) | 82.0 (75.9, 86.7) | 74.9 |
| 24 months | 67.7 (60.7, 73.8) | 64.0 (56.8, 70.2) | ≤55.6 |




*Reconstructed placebo data as if never treated with everolimus
RPST, rank preserving structural failure time

Yao et al. Ann Oncol 2014; 25 (suppl 4): abstr 1132O

# 1132O: Everolimus (EVE) for the Treatment of Advanced Pancreatic Neuroendocrine Tumors (pNET): Final Overall Survival (OS) Results of a Randomized, Double-blind, Placebo (PBO)-Controlled, Multicenter Phase III Trial (RADIANT-3) – Yao JC et al.

- **Key results (cont.)**

| AEs occurring in ≥30% in either group, % | Everolimus + BSC (n=207) | | Placebo + BSC (n=203) | |
|---|---|---|---|---|
| | All grades | Grade 3 or 4 | All grades | Grade 3 or 4 |
| **All** | **203 (99.5)** | **126 (61.8)** | **198 (97.5)** | **82 (40.4)** |
| Stomatitis | 110 (53.9) | 10 (4.9) | 27 (13.3) | 0 |
| Rash | 107 (52.5) | 1 (0.5) | 32 (15.8) | 0 |
| Diarrhoea | 98 (48.0) | 11 (5.4) | 48 (23.6) | 5 (2.5) |
| Fatigue | 91 (44.6) | 6 (2.9) | 54 (26.6) | 5 (2.5) |
| Oedema peripheral | 76 (37.3) | 2 (1.0) | 23 (11.3) | 2 (1.0) |
| Nausea | 67 (32.8) | 5 (2.5) | 66 (32.5) | 4 (2.0) |
| Pyrexia | 63 (30.9) | 2 (1.0) | 25 (12.3) | 1 (0.5) |
| Headache | 62 (30.4) | 1 (0.5) | 30 (14.8) | 2 (1.0) |

Yao et al. Ann Oncol 2014; 25 (suppl 4): abstr 1132O

# 1132O: Everolimus (EVE) for the Treatment of Advanced Pancreatic Neuroendocrine Tumors (pNET): Final Overall Survival (OS) Results of a Randomized, Double-blind, Placebo (PBO)-Controlled, Multicenter Phase III Trial (RADIANT-3) – Yao JC et al.

- **Conclusions**
  - Everolimus showed a clinically relevant 6.3-month longer mOS than placebo
    - 44.02 months vs. 37.68 months; HR 0.94; p=0.3
  - OS results may have been confounded by crossover of 85% of patients from the placebo arm to open-label everolimus
  - RPSFT analysis adjusting for crossover bias showed a survival benefit with everolimus vs. RPSFT-corrected placebo arm
    - 12-month OS 82.6% vs. 74.9%
    - 24-month OS 67.7% vs. 55.6%
  - The safety of everolimus was consistent with previous reports

Yao et al. Ann Oncol 2014; 25 (suppl 4): abstr 1132O

# 1134PD: Treatment satisfaction, symptom control, and quality of life (QoL) with lanreotide autogel (LAN) in neuroendocrine tumour (NET) patients with carcinoid syndrome (CS): Results from the SymNET study – Ruszniewski P et al.

- **Study objective**
  - To investigate HRQoL in patients with NET and carcinoid syndrome who received lanreotide Autogel
- **Study design**
  - SymNET was an observational study involving adults (aged ≥18 years) with a NET and a history of carcinoid syndrome-related diarrhoea who had been receiving lanreotide Autogel for >3 months
- **Key results**
  - A total of 273 patients were enrolled; 203/268 (76%) were completely/rather satisfied with diarrhoea control (primary endpoint); 107/146 (73%) were completely/rather satisfied with flushing control
  - EORTC QLQ-C30: functioning and global health status was good but fatigue, insomnia and diarrhoea were problematic
  - EORTC GI.NET21: disease-related worries and muscle/bone pain were the most problematic symptoms, as well as social functioning; a small number of patients found sexual function particularly problematic
- **Conclusion**
  - **Lanreotide Autogel was associated with good control of symptoms as well as high levels of patient satisfaction and HRQoL in patients with NET**

Ruszniewski et al. Ann Oncol 2014; 25 (suppl 4): abstr 1134PD

# 1135PD: Quality of life (QoL) associated with lanreotide autogel (LAN) treatment for carcinoid syndrome (CS) in gastroenteropancreatic neuroendocrine tumour (GEPNET) patients: Results of the ELECT study – Gomez-Panzani E et al.

- **Study objective**
  - To investigate rescue medication use and HRQoL outcomes with lanreotide Autogel in patients with GEP-NETs
- **Study design**
  - An initial double-blind and then open-label phase study in patients with GEP-NET (aged ≥18 years) and a history of carcinoid syndrome (diarrhoea/flushing) who received lanreotide Autogel 120 mg
- **Key results**
  - The ITT population comprised 114 patients
  - Compared with placebo, patients receiving lanreotide Autogel used 14.8% less days of rescue octreotide (p=0.02); there was no significant difference in daily frequency of diarrhoea, but flushing events were slightly higher for placebo (p=0.02)
  - QLQ-C30 scores were similar in lanreotide Autogel and placebo groups after 12 weeks
  - Slight improvements in endocrine (p=0.08) and GI (p=0.06) symptom scores on GI.NET21
- **Conclusion**
  - **In patients with GEP-NET, there was no deterioration in HRQoL with lanreotide Autogel; there was evidence of improvements in some domains of HRQoL**

Gomez-Panzani et al. Ann Oncol 2014; 25 (suppl 4): abstr 1135PD

# 1136PD: Quality of life (QoL) with lanreotide autogel (LAN) vs. placebo in patients with enteropancreatic neuroendocrine tumours (EP-NETs): Results from the CLARINET phase III study – Ruszniewski P et al.

- **Study objective**
  - To investigate the effect of lanreotide Autogel on HRQoL in patients with EP-NETs
- **Study design**
  - Post-hoc analyses were performed on the randomised, double-blind phase III CLARINET study in which patients with somatostatin receptor-positive NETs received lanreotide Autogel 120 mg (n=101) or placebo (n=103), once every 28 days, for 96 weeks (or until death or PD)
- **Key results**
  - 204 patients were included in the ITT population
  - HRQoL scores remained consistent throughout the study and were similar between lanreotide Autogel and placebo groups; similar results were observed with subscales scores of EORTC QLQ-C30 and QLQ-GI.NET21
  - In a multivariate analysis, sex, baseline global health status/QoL (≤75) and baseline hepatic tumour load (≤25%) were significant prognostic factors for changes in QoL
- **Conclusions**
  - **HRQoL was not adversely affected by lanreotide Autogel**
    - **Sex, baseline global health status/QoL and baseline hepatic tumour load are potential prognostic factors for changes in global health status/QoL**

Ruszniewski et al. Ann Oncol 2014; 25 (suppl 4): abstr 1136PD

## Poster discussion (1134PD, 1135PD and 1136PD) – Oberg K

- The three studies that assessed lanreotide Autogel treatment in patients with GEP-NET have confirmed previous studies showing good tolerability of somatostatin analogues
- The CLARINET and ELECT studies, in which patients were randomised to somatostatin autogel or placebo, did not show any deterioration in QoL
- The CLARINET study demonstrated potential prognostic factors for global health status/QoL changes during treatment including:
  - Sex: female vs. male
  - Hepatic tumour load: >25% vs. <25%
  - Baseline global health
  - Status/QoL score: >median vs. <median

# CANCER OF UNKNOWN PRIMARY

## 1137PD: Carcinoma of unknown primary: Features and outcomes of patients managed in a large UK centre – Lee R et al.

- **Study objective**
  - To identify features and examine prognosis of patients with carcinoma of unknown primary (CUP)
- **Study design**
  - Retrospective cohort study of patients with CUP between 2005 and 2011
- **Key results**
  - CUP was suspected in 249 patients; 134 were histologically confirmed
    - Median age at diagnosis was 64.5 (range 19–85) years
    - Median OS for confirmed CUP was 23.9 (range 0.14–441) weeks
  - OS, compared with BSC (4 weeks), was significantly better in those who had surgery (213 weeks; $p<0.001$), chemotherapy (32 weeks; $p<0.001$) or radiotherapy (34 weeks)
  - Median OS was greater among those achieving clinical benefit (PR/CR/SD; 57.1 versus 26.4 weeks; $p=0.001$)
- **Conclusions**
  - **Diagnosis and treatment of CUP is complex**
  - **Outcomes were better in those with squamous cell carcinoma, good performance status, no liver metastases and predominant lymph node involvement; responses in those undergoing surgery were durable**
  - **Benefit with chemotherapy was small**

Lee et al. Ann Oncol 2014; 25 (suppl 4): abstr 1137PD

# 1138PD: Activation status and prognostic significance of the Wnt/B catenin and Hedgehog/Smoothened signalling pathways in patients with cancer of unknown primary (CUP): A translational research study of the Hellenic Cooperative Oncology Group (HeCOG) – Pentheroudakis G et al.

- **Study objective**
  - To identify pathological features and prognostic factors in patients with cancer of unknown primary (CUP)
- **Study design**
  - Immunohistochemical expression of β-catenin and smoothened (SMO), plus the transcription factors TCF, LEF and GLI1 were examined in 87 patients with CUP and correlated with PFS and OS
- **Key results**
  - Median OS was significantly greater with SMO expression (19 vs. 12 months for SMO-negative cases; p=0.01)
  - Activated Wnt pathway (any expression of nuclear β-catenin, TCF or LEF) was associated with significantly increased PFS (median 9 vs. 5 months, p=0.037) and OS (median 19 vs. 13 months, p=0.04); the change in OS was mainly driven by nuclear expression of TCF and/or LEF (p=0.03)
  - Tumour nuclear staining for TCF/LEF was prognostic of OS (HR 0.15; p=0.018)
- **Conclusions**
  - **Wnt or Hedgehog pathways were activated in 25–33% of cases**
    - **An activated Wnt pathway was marginally associated with response to chemotherapy in CUP adenocarcinomas only**
    - **Nuclear SMO and an activated Wnt pathway was a favourable prognostic factor in CUP**

Pentheroudakis et al. Ann Oncol 2014; 25 (suppl 4): abstr 1138PD

# 1139PD: Clinical outcomes from the UK CUP-ONE Study: A multi-centre trial to assess the efficacy of epirubicin, cisplatin and capecitabine (ECX) in carcinomas of unknown primary (CUP) with prospective validation of molecular classifiers – Wasan HS et al.

- **Study objective**
  - To validate molecular diagnostic techniques and QoL in patients with carcinomas of un known primary (CUP)
- **Study design**
  - CUP-ONE was a combined translational and prospective treatment study; in the treatment phase patients with CUP received epirubicin, cisplatin and capecitabine
- **Key results**
  - Interim results were available for 58 patients
  - The most common grade 3/4 non-haematological AE was lethargy (reported in 14% of patients); neutropenia (grade 3 17%, grade 4 9% of patients) was the most common haematological AE
  - The best ORR was 35% (90% CI 26, 46); up to 25% of patients had additional/continued responses beyond 12 weeks
  - Median PFS was 30 weeks (80% CI 25, 33); median OS was 44 weeks (80% CI 36, 48); two-year survival estimate was 12% (80% CI 5, 18)
- **Conclusion**
  - **Combined epirubicin, cisplatin and capecitabine had efficacy and was well tolerated in patients with CUP**

Wasan et al. Ann Oncol 2014; 25 (suppl 4): abstr 1139PD

## Poster discussion (1137PD, 1138PD, 1139PD) – Skogseid B

- CUPs represent 4–5% of invasive tumours and 10–13% of NETs
- Very poor prognosis: OS ~1 year
- CUPs are heterogeneous with highly variable biology, making data interpretation difficult
- Nuclear SMO / Wnt pathway activation were favourable prognostic factors (1138PD)
  - Validation in larger cohorts seems prudent
- Patients who had surgery had durable response, therefore, it is important to consider surgery if feasible (1137PD)