

ESMO 2014 Congress Scientific Meeting Report – Gastrointestinal Cancers Extract

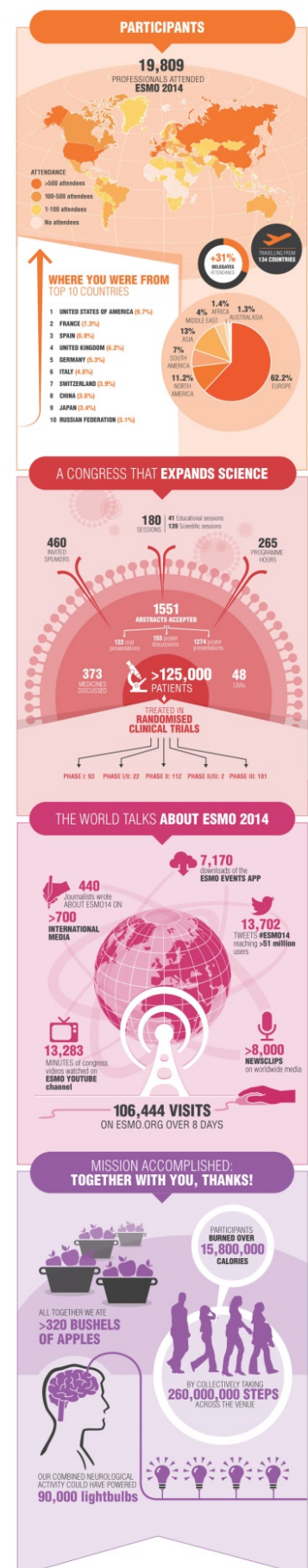
26-30 September 2014

Madrid, Spain

Summary

The European Society for Medical Oncology (ESMO) Congress, held September 26 to 30 in Madrid, Spain, was a record-breaker on nearly all levels. It was resounding success and in a dedicated infographic you can find the congress statistics. A primary emphasis in the scientific programme was placed on precision medicine and how it will change the future treatment landscape in oncology. In addition, a number of scientific presentations were dedicated to cancer immunology and immunotherapy across multiple tumour types. This report is an overview of key scientific presentations made during the congress by leading international investigators. It attempts to represent the diversity and depth of the ESMO 2014 scientific programme, as well as advances in oncology.

Infographic (right): ESMO 2014 record breaking Congress



Contents

Gastrointestinal Cancers.....	3
A phase IB study of pembroluzumab in patients with advanced gastric cancer	3
REACH: Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib	3
Axitinib plus best supportive care in patients with advanced hepatocellular carcinoma following prior antiangiogenic therapy	6
Optimal treatment strategy with anti-EGFR or anti-VEGF treatments in first-line RAS wild type metastatic CRC patients.....	9
CALGB/SWOG 80405: Phase III trial of FOLFIRI or mFOLFOX6 with bevacizumab or cetuximab for patients with expanded RAS analyses in untreated metastatic adenocarcinoma of the colon or rectum	9
Independent radiological evaluation of ORR, early tumour shrinkage, and depth of response in the FIRE-3 study: Analysis in the final RAS evaluable population	11
Data interpretation	13
TAS-102 improves OS and PFS in patients with metastatic CRC refractory to standard therapies	14
Bevacizumab/erlotinib as maintenance therapy in metastatic CRC: Final results of the GERCOR DREAM study.....	16
Final results from QUASAR2, a multicentre, international randomised phase III trial of capecitabine plus/minus bevacizumab in the adjuvant setting of stage II/III CRC	17
RELATED INFORMATION	19
Save the date	19
Affiliations and Disclosure	19
Acknowledgment.....	19

Gastrointestinal Cancers

A phase Ib study of pembrolizumab in patients with advanced gastric cancer

In a phase Ib study the researchers assessed the safety, tolerability, and antitumour activity of pembrolizumab in gastric cancer patients. The results were presented by Dr Kei Muro of the Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan. Pembrolizumab was generally well tolerated and provided antitumour activity in patients with advanced gastric cancer that expressed PD-L1.

Using a prototype immunohistochemistry (IHC) assay, PD-L1 expression was assessed in archival tumour samples from patients with recurrent/metastatic adenocarcinoma of the stomach or gastroesophageal junction. Eligible patients with PD-L1 staining in stroma or $\geq 1\%$ of tumour cells were enrolled and treated with pembrolizumab every 2 weeks for up to 24 months or until complete response (CR), disease progression, or unacceptable toxicity.

Enrolment was designed to include an equal number of patients from Asia Pacific and the rest of the world. Adverse events were monitored and graded per the NCI CTCAE v4.0. Radiographic imaging was performed every 8 weeks. Primary efficacy endpoint was ORR assessed by RECIST v1.1.

Of the 162 patients screened, 65 (40%) were PD-L1-positive of which 39 enrolled: 19 from Asia Pacific, 20 from rest of world. Median age was 63 years, and 72% of patients were men. Patients from Asia Pacific were more heavily pretreated than patients from rest of world (≥ 2 prior therapies in 79% vs. 55%). Median follow-up duration was approximately 6 months.

The most common adverse events deemed treatment-related by investigators were hypothyroidism and fatigue. Grade ≥ 3 adverse events deemed treatment-related occurred in 3 patients (1 each for hypoxia, peripheral neuropathy, and pneumonitis).

The ORR (confirmed and unconfirmed) was 31.6% in Asia Pacific and 30% in the rest of world. Responses were ongoing for 6 of 6 Asia Pacific patients and 5 of 6 patients from the rest of world (median response duration not reached; range 8+ to 20+ weeks).

Evidence of an association between PD-L1 expression and PFS ($p = 0.032$) and ORR ($p = 0.071$) was observed. Preliminary data correlating PD-L1 expression with clinical outcomes will be further explored.

The robust antitumour activity observed supports the further development of pembrolizumab in advanced gastric cancer.

The study was supported by Merck Sharp & Dohme Corp.

Reference

LBA15: A phase 1b study of pembrolizumab (Pembro; MK-3475) in patients (Pts) with advanced gastric cancer

REACH: Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib

The results of the REACH randomised, phase III study were presented by Prof. Andrew Zhu of the Massachusetts General Hospital Cancer Center, Boston, USA. The study primary endpoint was not met, but in a selected population of patients with an elevated baseline α -fetoprotein (AFP), a

meaningful OS improvement in the ramucirumab arm was observed. The treatment was well tolerated and demonstrated an acceptable safety profile. Given the high unmet medical need for second-line treatment in hepatocellular carcinoma, further investigation of ramucirumab might be warranted.

Sorafenib is the only approved first-line treatment in hepatocellular carcinoma. No treatment has demonstrated a survival benefit in the second-line setting. Vascular endothelial growth factor (VEGF) and VEGF-receptor 2-mediated signalling and angiogenesis likely contribute to pathogenesis of hepatocellular carcinoma.

Ramucirumab is a fully human IgG1 monoclonal antibody that binds to extracellular domain of VEGFR-2, preventing ligand binding and receptor activation. Preliminary evidence of ramucirumab anticancer activity in treatment-naïve hepatocellular carcinoma was demonstrated in a single-arm phase II study.

The REACH study evaluated the safety and efficacy of ramucirumab in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib.

It was required that patients eligible for the study have advanced hepatocellular carcinoma (histological or radiographical imaging confirmation) in stage BCLC C or B, who are refractory or not amenable to loco-regional therapy, have Child-Pugh A, ECOG PS 0 or 1, intolerance to sorafenib despite dose reduction, or disease progression during or following sorafenib, and adequate haematologic and biochemical parameters.

Patients were randomised 1:1 to receive ramucirumab i.v. plus best supportive care or placebo plus best supportive care every 2 weeks until disease progression, unacceptable toxicity, or death.

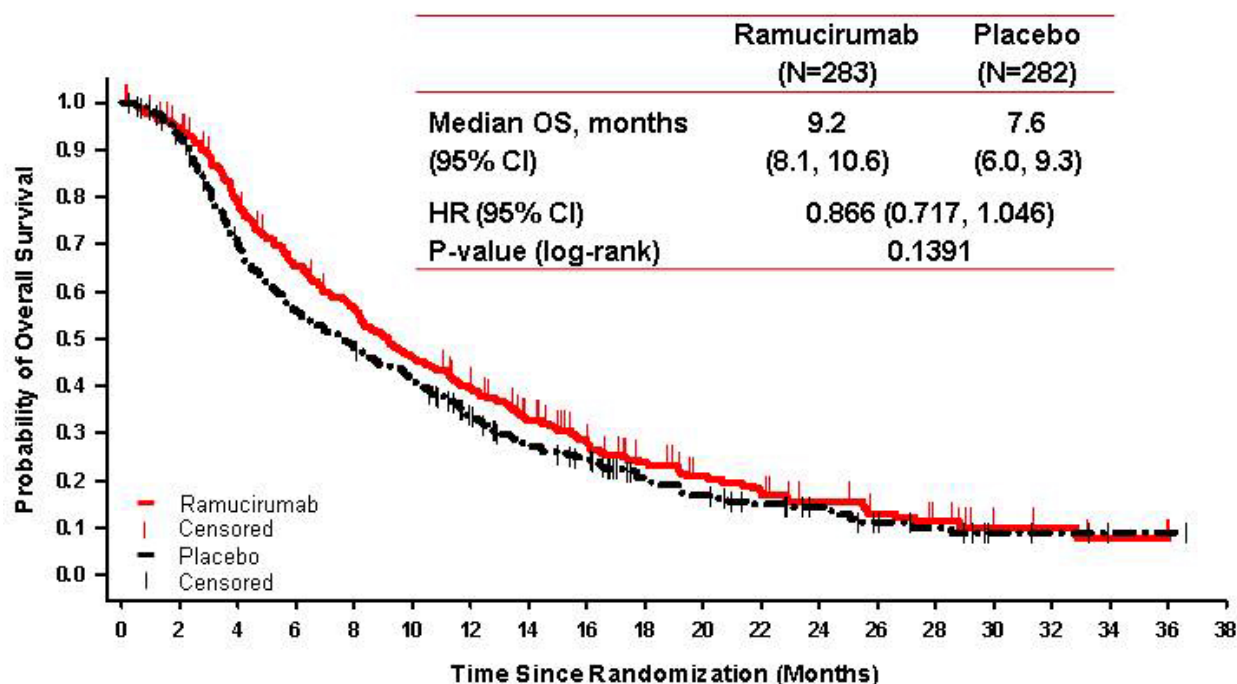
The primary endpoint was OS. Secondary endpoints included PFS, time to progression, ORR, safety and patient reported outcomes.

The sample size of 544 patients was calculated to enable 85% power to demonstrate statistical significance at an overall two-sided α of 0.05, assuming a HR of 0.75 and OS improvement from 8 to 10.67 months in the ramucirumab arm.

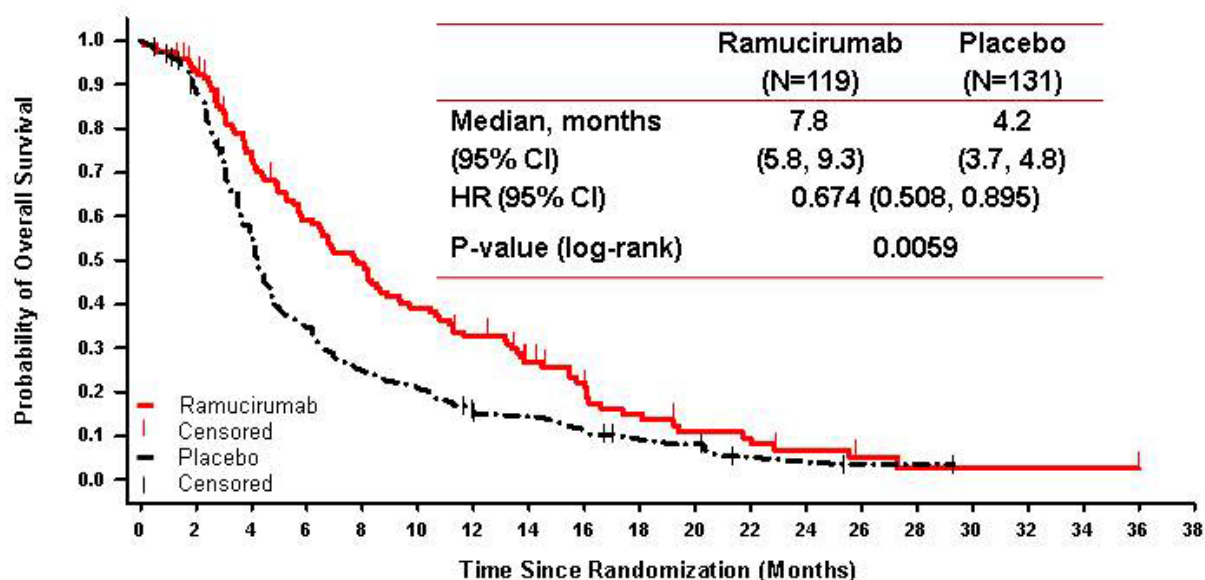
Between November 2010 and April 2013, 565 ITT patients were randomised: 283 in the ramucirumab arm and 282 in the placebo arm. Baseline patient characteristics were balanced between the two arms.

In the ITT population, the OS HR was 0.866 ($p = 0.1391$); median OS was 9.2 months for the ramucirumab arm vs. 7.6 months for the placebo arm. Forest plot of OS by subgroup favoured ramucirumab.

Overall Survival in Hepatocellular Cancer Patients ITT Population



Overall Survival in Hepatocellular Cancer Patients Baseline Alpha-fetoprotein ≥ 400 ng/mL



Caption: OS in the study ITT population and in patients with baseline α -fetoprotein ≥ 400 ng/mL. © Andrew Zhu

Median PFS in the ITT population with ramucirumab was 2.8 months and 2.1 months with placebo, respectively (HR 0.63, $p < 0.0001$) with forest plot by subgroup in favour of ramucirumab.

Median time to progression was 3.48 months in the ramucirumab arm vs. 2.63 months in the placebo arm ($p < 0.0001$). The ORR was 7.1% in the ramucirumab arm and 0.7% in the placebo arm ($p < 0.0001$).

In 250 patients with baseline α -fetoprotein (AFP) ≥ 400 ng/mL which was pre-specified, OS HR was 0.67 ($p = 0.0059$) with median OS of 7.8 months for ramucirumab vs. 4.2 months for placebo.

The safety population comprised 553 patients (277 patients in the ramucirumab arm and 276 patients in the placebo arm). No new safety signals were observed. However, grade ≥ 3 adverse events occurring in $>5\%$ of treated ramucirumab patients included: hypertension (12.3% in the ramucirumab arm vs. 3.6% in the placebo arm), asthenia (5.1% vs. 1.8%), aspartate aminotransferase increase (5.4% vs. 8.3%), and malignant neoplasm progression (6.5% vs. 4.0%).

The study was sponsored by Eli Lilly.

Reference

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

Axitinib plus best supportive care in patients with advanced hepatocellular carcinoma following prior antiangiogenic therapy

Prof. Yoon-Koo Kang of the Department of Oncology, Asan Medical Center, Seoul, Korea presented results of a study with axitinib plus best supportive care vs. placebo plus best supportive care in patients with advanced hepatocellular carcinoma following prior antiangiogenic therapy.

Sorafenib, multi-targeted tyrosine kinase inhibitor (TKI) is the current standard treatment for advanced hepatocellular carcinoma. It prolonged OS over placebo in patients with advanced disease. However, other molecular targeted agents failed to show survival benefit in first- or second-line hepatocellular carcinoma. Therefore, an unmet need exists for treatment of patients who progressed on or are intolerant to sorafenib.

The efficacy and safety of axitinib, a potent and selective inhibitor of VEGF receptors 1-3, was evaluated in this global, randomised, double-blind phase II clinical trial in patients with locally-advanced or metastatic hepatocellular carcinoma.

Eligible patients who progressed on or were intolerant to one prior antiangiogenic therapy, Child-Pugh Class A or B (score 7 only) and ECOG PS 0 or 1 were randomised 2:1 to receive axitinib plus best supportive care or placebo plus best supportive care. They were stratified by tumour invasion defined as a presence vs. absence of extrahepatic spread and/or vascular invasion, and geographic region (Asia vs. non-Asia).

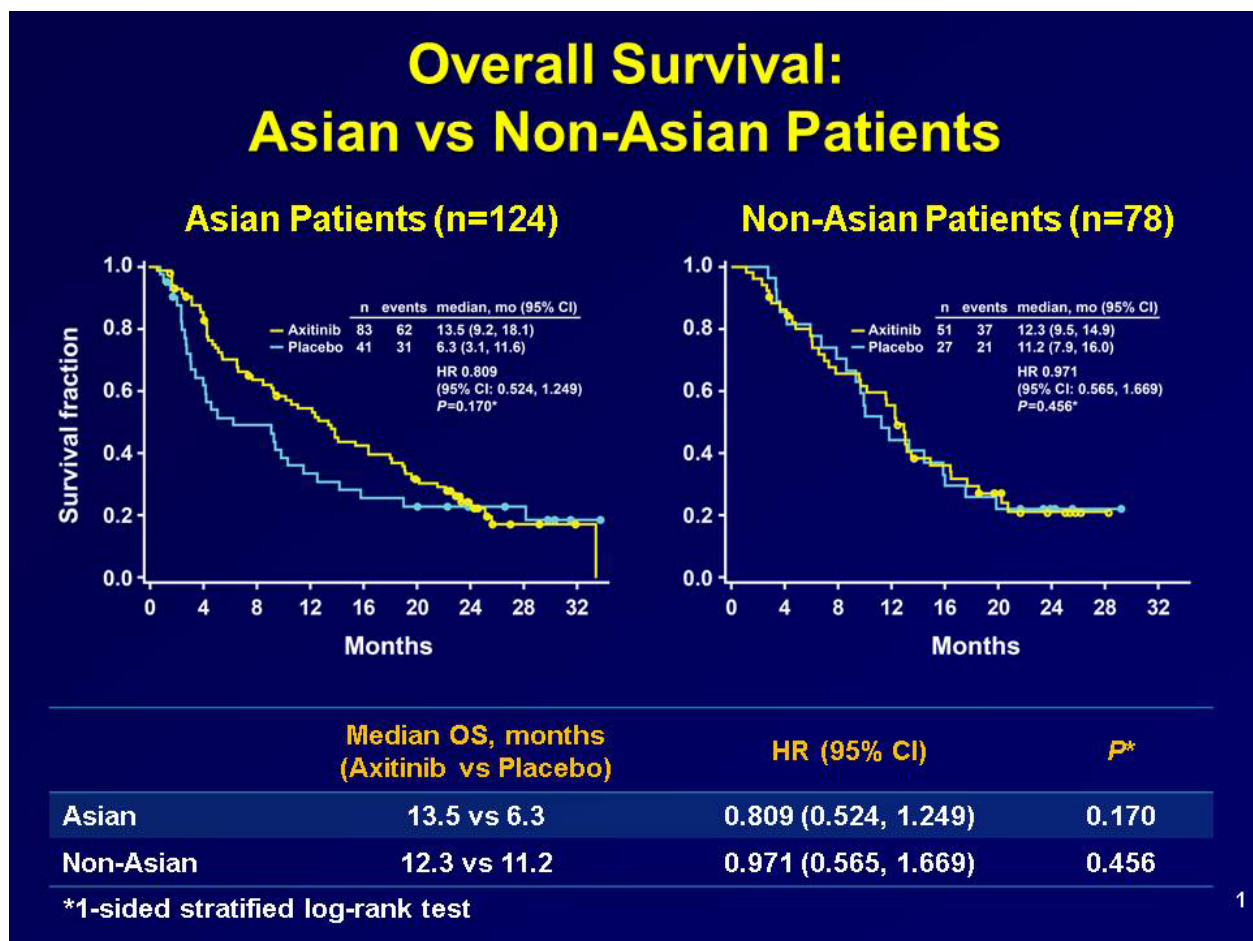
The primary endpoint was OS and secondary endpoints included PFS, time to progression, ORR, DoR, disease control rate (DCR), safety, health related QoL and biomarkers.

The study had 80% power to detect an improvement in median OS from 5.0 to 8.3 months with axitinib plus best supportive care, corresponding to a HR 0.60 (1-sided $\alpha = 0.025$).

To achieve the targeted number of 150 events (deaths) for final analysis, 198 patients had to be enrolled. From December 2010 to July 2012, 202 patients were randomised. An interim analysis was performed after approximately 50% of OS events occurred. The Independent Data Monitoring Committee recommended to proceed as per plan. As of the data cut-off for primary analysis (3 March 2014) 151 events were reported with 29 patients alive, 8 on treatment (axitinib 7 vs. placebo 1).

Two hundred two patients were randomised (134 in the axitinib arm and 68 in the placebo arm). They were predominantly of Asian origin (63% vs. 62%). Baseline patient characteristics and stratification factors were well balanced between the axitinib vs. placebo arms. All patients had Child-Pugh A category and 76% of patients in both arms had tumour invasion.

Median OS with axitinib was 12.7 months vs. 9.7 months with placebo, a difference that was not statistically significant (HR 0.870; $p = 0.211$). In Asian patients median OS was 13.5 months vs. 6.3 months in non-Asian, but this difference was not statistically significant either.

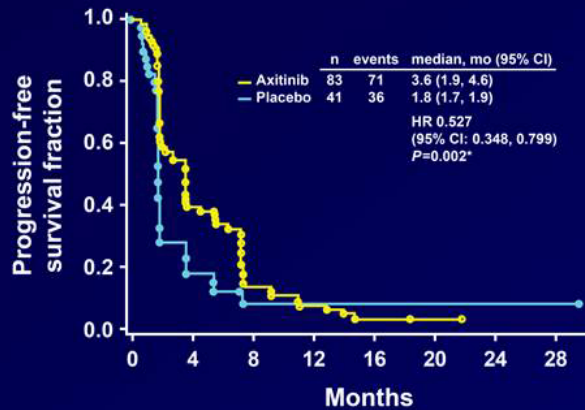


Caption: OS in Asian vs. non-Asian patients. © Yoon-Koo Kang

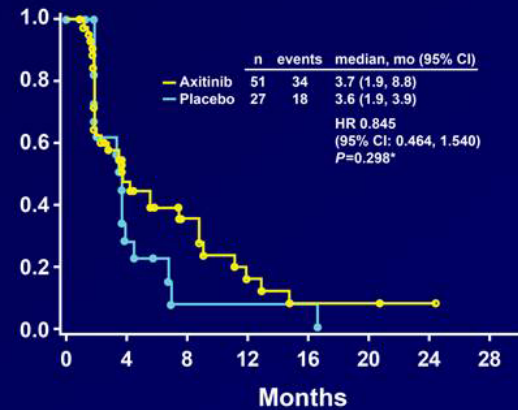
Investigator-assessed median PFS in all randomised patients was 3.6 months with axitinib vs. 1.9 months with placebo and was statistically significant (HR 0.618; $p = 0.004$). The difference between PFS in Asian patients vs. non-Asian was statistically significant too, 3.6 vs. 1.8 month (HR 0.527, $p = 0.002$).

Progression-Free Survival: Asian vs Non-Asian Patients

Asian Patients (n=124)



Non-Asian Patients (n=78)



	Median PFS, months (Axitinib vs Placebo)	HR (95% CI)	P*
Asian	3.6 vs 1.8	0.527 (0.348, 0.799)	0.002
Non-Asian	3.7 vs 3.6	0.845 (0.464, 1.540)	0.298

*1-sided stratified log-rank test

Caption: PFS in Asian vs. non-Asian patients. © Yoon-Koo Kang

The ORR was 9.7% with axitinib vs. 2.9% with placebo (p = 0.083).

Overall DCR was 31.1% vs. 11.8% in favour of axitinib treated patients (p = 0.002).

Safety profile with axitinib was consistent with earlier clinical trials and no new safety signal was detected. However, more patients discontinued treatment due to adverse events with axitinib vs. placebo.

Most common all cause adverse events in axitinib vs. placebo group were: diarrhoea (54% vs. 12%), hypertension (54% vs. 13%), decreased appetite (47% vs. 21%), fatigue (35% vs. 26%), abdominal pain (34% vs. 21%), hand-foot syndrome (34% vs. 6%), weight decrease (27% vs. 3%), nausea (26% vs. 10%), dysphonia and hypothyroidism (25% vs. 0% each).

Grade ≥ 3 adverse events were higher in the axitinib group: diarrhoea (20% vs. 0%), hypertension (26% vs. 1%), and hand and foot syndrome reaction (15% vs. 0%).

The authors concluded that axitinib plus best supportive care did not demonstrate statistically significant improvement in median OS but improved median PFS when compared with placebo plus best supportive care in patients with advanced hepatocellular carcinoma who received prior antiangiogenic therapy. Regional differences in the efficacy were noticeable.

The study was sponsored by Pfizer Inc.

Dr Michel Ducreux of the Institut Gustave Roussy, Villejuif, France, who discussed the results from two above studies, said that there is something there but the researchers were unable to

demonstrate it because hepatocellular carcinoma is an entity of different diseases with different biological pathways and different clinical features.

Reference

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

Optimal treatment strategy with anti-EGFR or anti-VEGF treatments in first-line RAS wild type metastatic CRC patients

During the special session at ESMO 2014 on defining the optimal treatment strategy with anti-EGFR or anti-VEGF treatments in first-line RAS wild type metastatic CRC patients, the CALGB/SWOG 80405 researchers presented long awaited results of OS in all RAS wild type population, while FIRE-3 study researchers presented independent radiological evaluation of ORR, early tumour shrinkage, and depth of response in the final RAS evaluable population.

The session was moderated by Dr Dirk Arnold and the data were discussed by doctors Andres Cervantes, Alberto Sobrero, and Fortunato Ciardiello.

CALGB/SWOG 80405: Phase III trial of FOLFIRI or mFOLFOX6 with bevacizumab or cetuximab for patients with expanded RAS analyses in untreated metastatic adenocarcinoma of the colon or rectum

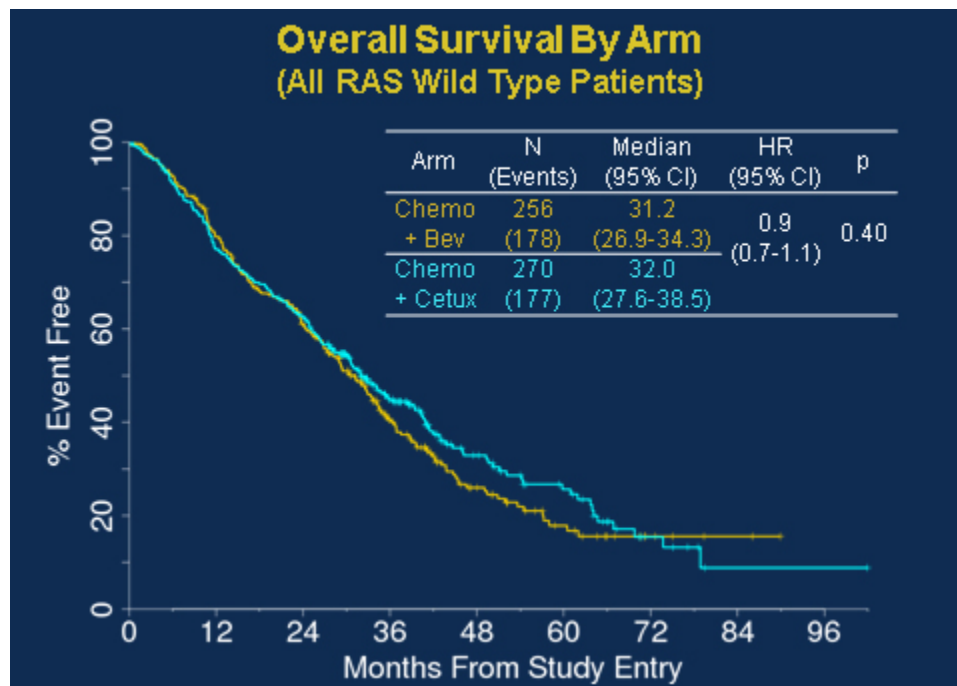
Dr Heinz-Josef Lenz of the Division of Medical Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, USA presented results of expanded RAS analysis in the CALGB/SWOG 80405 study. Earlier this year, the study researchers presented the findings concluding that FOLFIRI/cetuximab and mFOLFOX6/bevacizumab are equivalent in terms of OS in patients with previously untreated KRAS wild type (codons 12 and 13) metastatic CRC and that either regimen is appropriate in first-line treatment. The OS of longer than 29 months and 8% of long-term survivors confirmed the progress in this setting. However, the oncology community expected that expanded RAS and other molecular and clinical analyses could identify subsets of patients who get more or less benefit from specific regimens.

The original CALGB/SWOG 80405 study included unselected patients with metastatic CRC who received treatment according to physician-selected chemotherapy (FOLFIRI or mFOLFOX6) and were randomised to cetuximab, bevacizumab or both (the third arm was subsequently closed). After 1420 patients were accrued the study was amended as following: only patients with wild type KRAS tumours (codon 12 and 13) were included. Accrual goal was 1142 patients.

Between November 2005 and March 2012, 3058 unselected patients were enrolled and 2334 KRAS wild type patients randomised. The final number included 1137 patients (333 pre-amend eligible retrospective KRAS test, and 804 post-amend).

Expanded RAS was tested in all wild type RAS exon 2 using beaming technology including KRAS exon 3,4 and NRAS exon 2, 3 and 4 with a detection sensitivity of 0.01%. The primary endpoint was OS.

In expanded the RAS wild type population, the median OS was pushed beyond 30 months. However, there was no significant difference between the cetuximab and bevacizumab in combination with chemotherapy (32 months vs. 31.2 months).



Caption: OS in all RAS wild type patients in CALGB/SWOG 80405 study. © Heinz-Josef Lenz

There was no difference in the PFS either. However, there was higher response achieved in the cetuximab arm in the expanded RAS population, 68.6% vs. 53.6% ($p < 0.01$).

In a separate analysis from the study of KRAS wild type patients undergoing surgery as a part of treatment strategy, the goal of which was to determine the characteristics and the long-term outcome of patients enrolled in the trial, Dr Alan Venook of the Division Of Medical Oncology, University of California, San Francisco, USA reported that 130 patients enrolled reached a stage of non evidence of disease (NED) after chemotherapy and surgery. The median OS in these patients was 60 months although many have recurred.

However, at the time of the abstract submission, the study researchers anticipated evaluation of all RAS status and planned an analysis in the subset of patients who underwent surgery to identify possible predictive characteristics but also to determine if there is an explanation for the fact that more patients on cetuximab went to surgery than patients on bevacizumab. During the session, Dr Venook reported that patients were likelier to reach NED stage on cetuximab but the ultimate outcome seems to be similar.

The trial lead organizations/sponsors were the Cancer and Leukemia Group B (CALGB), USA National Cancer Institute, and Southwest Oncology Group (SWOG).

Reference

5010: 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 or rectum (mCRC)

Independent radiological evaluation of ORR, early tumour shrinkage, and depth of response in the FIRE-3 study: Analysis in the final RAS evaluable population

Based on an independent radiological review, FOLFIRI plus cetuximab induced a significantly higher ORR, a greater rate of early tumour shrinkage (ETS), and an increased depth of response (DpR) compared to FOLFIRI plus bevacizumab. These response-related outcomes may in part explain the significant OS advantage of FOLFIRI plus cetuximab treatment observed in the extended RAS wild type study population. The findings were reported by Dr Sebastian Stintzing of the University of Munich, Department of Hematology and Oncology.

The FIRE-3 study, performed in 150 centres in Germany and Austria, compared first-line therapy with FOLFIRI plus either cetuximab or bevacizumab (1:1) and was amended in October 2008 to include only KRAS wild-type patients. The study was conducted in 592 KRAS exon 2 wild-type metastatic CRC patients. Extended RAS analysis was carried out in KRAS and NRAS exon 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) using pyro-sequencing technique.

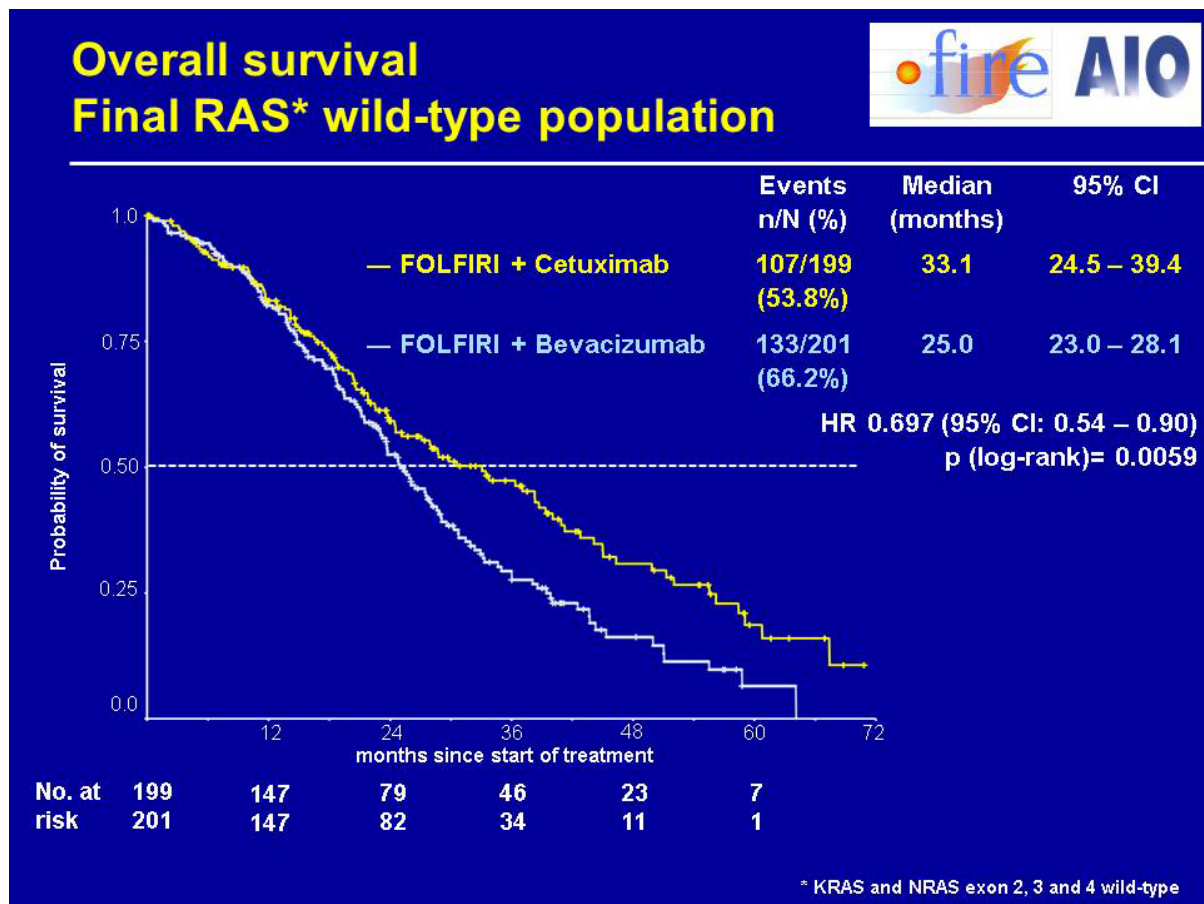
An independent radiological review was performed to evaluate tumour response according to RECIST v1.1 and to define ETS and DpR. Reviewers were blinded to patient data.

ETS was defined as a reduction in tumour diameter of more than 20% at first-tumour assessment after baseline (week 6). DpR was defined as the maximal tumour shrinkage observed at the nadir compared with baseline.

Calculations were done for both the ITT and the extended RAS wild-type population. At ESMO 2014, Dr Stintzing presented data from the analysis in final RAS evaluable patients.

Independent evaluation in KRAS exon 2 wild type population showed an ORR of 66.5% in the cetuximab arm and 55.6% in the bevacizumab arm ($p = 0.016$). In the final RAS wild type population, the ORR was 72% in the cetuximab arm vs. 56.1% in the bevacizumab arm ($p = 0.003$).

The OS favoured the cetuximab arm, 33.1 months vs. 25.0 months (HR 0.697, $p = 0.0059$).



Caption: OS in the final RAS wild type population in the FIRE-3 study. © Sebastian Stintzing

In the final RAS wild type population, PFS in patients with ETS in the cetuximab arm was 9.7 months vs. 5.8 months in patients with no-ETS. In the bevacizumab arm the PFS in ETS patients was 11.7 months vs. 8.3 months in non-ETS patients.

DoR correlated significantly with OS and PFS ($p = 0.0003$ in KRAS exon 2 wild-type patients and $p < 0.0001$ in the final RAS wild type population).

Median time to tumour nadir in the cetuximab arm was 15.0 weeks and 15.7 weeks in the bevacizumab arm.

Dr Stintzing said that extended RAS testing was possible in $> 80\%$ of FIRE-3 ITT population. He concluded that median OS was markedly superior in all-RAS wild type patients receiving first-line therapy with cetuximab. The independent radiology review demonstrated a significantly higher ORR in FOLFIRI plus cetuximab treated patients compared to those receiving FOLFIRI plus bevacizumab. The ETS was significantly more frequent in the cetuximab arm, and it was significantly associated with prolonged survival independent of the treatment arm. Median DoR was significantly greater in the cetuximab arm and correlated with survival.

FIRE-3 was an investigator sponsored study. The study collaborator was Merck KGaA.

Reference

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

Data interpretation

Prof. Andres Cervantes of the University Hospital, Valencia, Spain addressed the following two important questions:

Why are the OS results discordant in these two trials?

A detailed information on second- and further line therapies is needed. In particular, the proportion of patients randomised to chemotherapy plus bevacizumab who never got cetuximab could be of importance to interpret these results. In a setting where more than 80% of patients get second-line therapy, it could imply that the sequence of treatments would not be relevant for OS. However, if the proportion of patients missing cetuximab in second-line is higher, the sequence of treatments could be very relevant.

What is the relevance of having a higher response rate in cetuximab containing regimens?

Chemotherapy plus bevacizumab or plus cetuximab are two potential options to start treatment in all RAS wild type advanced CRC patients. But, how does the fact that a higher response rate with cetuximab containing regimens influence decisions in selecting initial therapeutic approach? The CALGB 80405 data on response rate has to be further analysed in respect to depth of response and early tumour shrinkage. This could be an important point to communicate with patients when taking therapeutic decisions.

Dr Alberto Sobrero of the IRCCS AOU San Martino - IST-Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy, said that the FIRE-3 study shows internal consistency and strengthened plausibility while the CALGB researchers presented early data analysis from a trial performed over 10 years. Therefore, he would wait for complete data before conclusion.

Prof. Dirk Arnold of the Clinic for Tumour Biology, Freiburg, Germany, said that patients with RAS wild type do (slightly) better with anti-EGFR therapies. However, many open questions remain: why is this so, will further information of treatment characteristics (e.g. duration and second-line treatments) really change clinical view on the data?

RAS is important, but taken alone it is not a great positive predictive biomarker. Any of the combinations used is an excellent option and should be part of the first-line treatment as OS is longer than 31 months. Presumably, the first-line choice is not that important for most patients (maybe except need for early tumour shrinkage and depth of response).

According to Prof. Fortunato Ciardiello of the Seconda Università Studi di Napoli Policlinico Federico II, Naples, Italy, who was one of discussants in the session, metastatic CRC is a heterogenous disease. A subset of metastatic CRC is highly dependent on EGFR signalling. KRAS and NRAS testing are the first step to identifying those patients that could benefit from anti-EGFR monoclonal antibodies treatment.

All metastatic CRC patients should have extended RAS testing before first-line treatment choice to offer them all available therapeutic opportunities.

Patients with RAS wild type cancer have two good therapeutic options that should be offered sequentially in first- and second-lines (FOLFOX or FOLFIRI plus either anti-EGFR monoclonal antibodies or bevacizumab).

In his opinion, FOLFIRI or FOLFOX with an anti-EGFR antibody is the preferred first-line choice if tumour shrinkage is a relevant therapeutic goal (high tumour burden, symptomatic disease, potential conversion to surgical resection of liver metastases or, possibly, of the primary tumour).

Tolerability, side effects and informed discussion with the patient could be important aspects for first-line choices.

For Prof. Ciardiello, open issues for clinical and translational research on how to optimise therapeutic management of metastatic CRC patients with RAS wild type tumours are:

- Role of maintenance; chemotherapy depotentiation; reintroduction of chemotherapy.
- Role of appropriate sequencing of bevacizumab and anti-EGFR monoclonal antibodies.
- Strategies to prevent/overcome acquired resistance to anti-EGFR monoclonal antibodies and to bevacizumab.

TAS-102 improves OS and PFS in patients with metastatic CRC refractory to standard therapies

A final analysis of primary endpoints from the phase III RECOURSE study in patients with metastatic CRC refractory to standard therapies showed a statistically significant OS and PFS benefit with TAS-102 in all prospectively defined subgroup analyses, including prior therapy with regorafenib. The results were presented by Prof. Eric Van Cutsem of the Digestive Oncology Unit, University Hospital Leuven, Leuven, Belgium.

The data from the RECOURSE study was first reported at the ESMO World Congress in GI Cancer earlier this year in Barcelona, Spain. At ESMO 2014, Prof. Van Cutsem presented new data, in particular subgroup analyses of OS and PFS by KRAS status, stratification factors and patient characteristics, and time to worsening of ECOG PS to 2 or more.

TAS-102 is a combination of a novel oral nucleoside, trifluridine (FTD) with the thymidine phosphorylase inhibitor, tipiracil hydrochloride (TPI), which prevents the degradation of FTD, enabling sustained and effective FTD levels.

RECOURSE was conducted to evaluate the efficacy and safety of TAS-102 in patients with mCRC refractory to standard therapies. Patients with ECOG PS 0-1 who had failed two or more prior treatments with fluoropyrimidines, irinotecan, oxaliplatin, bevacizumab and cetuximab/panitumumab (in case of KRAS wild-type disease) were eligible for the study.

Treatment continuation was foreseen until progression, intolerant toxicity or patient refusal. It was a multicenter, randomised, double-blind, placebo-controlled, phase III study with stratification by KRAS status, time from diagnosis to metastatic disease, and geographical region. It was performed in 13 countries around the world. Enrollment started in June 2012 and finished in October 2013.

The study primary endpoint was OS and the key secondary efficacy endpoint was PFS. Other secondary endpoints included safety, tolerability, time to treatment failure (TTF), ORR, DCR, DoR, OS and PFS in subgroups determined by KRAS status.

The OS and PFS were evaluated by using univariate and multivariate analyses for prospectively defined subgroups and a retrospectively defined subgroup of patients with prior treatment with regorafenib.

In total 800 patients were randomised to TAS-102 (534 patients) or placebo (266 patients). In the ITT population, patient demographics and characteristics were balanced between the two arms with one third of Asian patients in each group.

The HRs for OS and PFS were 0.68 ($p < 0.0001$) and 0.48 ($p < 0.0001$), respectively, both favouring TAS-102. The OS in TAS-102 group was 7.1 month vs. 5.3 month in placebo group. Median PFS was 2.0 months in TAS-102 treated patients and 1.7 month in the placebo arm.

The OS and PFS benefit with TAS-102 was consistent across all subgroups. In particular, the HRs for OS in subgroups were 0.58 in patients with KRAS wild-type tumours and 0.80 in KRAS mutated tumours; 0.64 in Western population and 0.75 in Asian patients; 0.73 in patients with PS 0 and 0.61 in patients with PS 1; and 0.69 for patients who have already received or not regorafenib.

In patients with time from diagnosis to first metastasis shorter than 18 months, the HR for OS was 0.84 and 0.64 in those with ≥ 18 months. In patients younger than 65, this HR was 0.74 and 0.62 in the group ≥ 65 years old. In patients who received three prior treatments, the HR was 0.74 and 0.59 in those who received ≥ 4 treatment lines.

The OS treatment effect remained the same in the multivariate model. No predictive factors were identified. Statistically significant prognostic factors ($p < 0.05$) in final model based on stepwise selection were:

- time since diagnosis of first metastasis,
- ECOG PS,
- and number of metastatic sites.

Time to worsening of ECOG PS status to 2 or more was significantly delayed with TAS-102 vs. placebo with medians of 5.7 vs. 4.0 months (HR 0.66, $p < 0.0001$). Post-study treatment was similar between the arms (41.2% in TAS-102, 42.5% in placebo).

Safety results were previously presented at the ESMO World Congress on GI Cancer 2014. The most frequently observed toxicities were GI and haematologic. Serious adverse events were observed in 29.6% patients in TAS-102 and 33.6% patients in placebo group. Primary reason for treatment discontinuation due to adverse events was 3.6% in TAS-102 and 1.5% in the placebo group. One treatment-related death was observed in TAS-102 group. The rate of febrile neutropenia was 3.8% and frequency of G-CSF usage 9.4% in TAS-102 and 0% in placebo group.

Prof. Van Cutsem concluded that TAS-102 demonstrated a clinically relevant improvement in OS and PFS compared with placebo in patients with mCRC refractory/intolerant to standard therapies. Improved OS benefit was statistically significant or trended favorably for TAS-102 across all stratification factors and predefined subgroups. Consistent with OS results, PFS improvement for TAS-102 was statistically significant across all stratification factors and predefined subgroups. The OS benefit was maintained irrespective of regorafenib use.

Discussant Prof. Christophe Tournigand of the Hôpital Henri Mondor, Créteil, France, said that in the RECOURSE study TAS-102 significantly improved OS and PFS in patients with metastatic CRC, refractory or intolerant to standard therapies. However, questions for the future would be: identifying biomarkers, addressing the question of QoL improvement, and seeing efficacy/tolerance in combination therapy, and efficacy in earlier lines of therapy.

The sponsor of the study was Taiho Oncology Inc./Taiho Pharmaceutical Co. Ltd.

Reference

LBA13: Phase III RECURSE trial of TAS-102 vs. placebo, with best supportive care (BSC), in patients (pts) with metastatic colorectal cancer (mCRC) refractory to standard therapies

Bevacizumab/erlotinib as maintenance therapy in metastatic CRC: Final results of the GERCOR DREAM study

Dr Benoist Chibudel of the Institut Hospitalier Franco-Britannique, Levallois-Perret, France reported that combination of erlotinib and bevacizumab as maintenance therapy significantly prolonged PFS and OS in patients with unresectable metastatic CRC. The combination of anti-VEGF monoclonal antibody and EGFR TKI is active, even in mutated KRAS patients.

VEGF or EGFR targeted monoclonal antibodies with chemotherapy demonstrated clinical activity in metastatic CRC. Yet, combining these monoclonal antibodies in mCRC achieved adverse outcomes. However, erlotinib, an EGFR TKI, combined with bevacizumab as maintenance therapy after bevacizumab-based induction therapy improved PFS according to results presented at 2012 Congress of the American Society of Clinical Oncology (ASCO). At ESMO 2014, the researchers reported the final results of the DREAM study.

VEGF inhibition with bevacizumab or aflibercept increases survival in combination with oxaliplatin- or irinotecan-based chemotherapy in first- or second-line. EGFR inhibition (panitumumab or cetuximab) increases survival in patients with RAS wild-type tumours. Crosstalk between EGFR pathway and VEGF is involved in tumour growth and survival. Bevacizumab and erlotinib are more active than bevacizumab alone in three xenograft models. Quantitative IHC analysis showed that bevacizumab activated EGFR in the tumour cells and in the tumour-associated endothelial cells which was attenuated by erlotinib.

DREAM is a phase III trial in patients with unresectable metastatic CRC. Patients without progression or surgery after a bevacizumab-based induction therapy were randomised to bevacizumab or bevacizumab plus erlotinib as maintenance therapy until progression after stratification by centre, baseline ECOG PS, ALP, LDH, induction chemotherapy (XELOX2/bevacizumab vs. mFOLFOX7/bevacizumab or FOLFIRI/bevacizumab), KRAS status, age, number of metastatic sites and tumour response.

Primary endpoint was maintenance PFS from randomisation. Secondary endpoints were OS, PFS from registration, response according to KRAS status, adverse events, curative resection, chemotherapy-free interval, and QoL.

Among 701 registered patients, 452 were randomised for maintenance (228 in the bevacizumab arm; 224 in the bevacizumab/erlotinib arm). Median follow-up was 50 months.

In the bevacizumab arm vs. bevacizumab/erlotinib arm, medians were for maintenance PFS 4.9 vs. 5.9 months (HR 0.77; $p = 0.012$), PFS from registration 9.3 vs. 10.2 months (HR 0.76; $p = 0.007$), maintenance OS 22.1 vs. 24.9 months (HR 0.80; $p = 0.035$), OS from registration 26.9 vs. 30.5 months (HR 0.80; $p = 0.040$). All subgroups, including KRAS, had a benefit in OS.

Response rate from baseline maintenance were in the bevacizumab vs. bevacizumab/erlotinib arm: all patients 11.5% vs. 22.5% ($p = 0.003$), KRAS wild-type 15.4% vs. 24% ($p = 0.133$), KRAS mutated 8.3% vs. 19.7% ($p = 0.041$).

Patients in the bevacizumab arm vs. bevacizumab/erlotinib arm experienced less grade 3/4 diarrhoea (0.9% vs. 9.3%) and skin rash (0% vs. 21.4%).

Dr Axel Grothey of the Mayo Clinic, Rochester, USA who discussed the study results, said that he was skeptical at first of whether the trial design is scientifically valid, but the results validate it. There is heterogeneity of induction chemotherapy and bevacizumab alone is not the optimal control arm in maintenance. The results are not as expected, and they are still a bit puzzling (no effect of KRAS status, short duration of erlotinib, PFS HR is similar to OS HR). There is a need for confirmatory/additional studies. The results don't have implications for clinical practice, as there is a need for confirmatory results. The results also don't have yet implications for future clinical trials.

This was investigator led study. The study sponsor was GERCOR.

Reference

4970: Bevacizumab-erlotinib as maintenance therapy in metastatic colorectal cancer. Final results of the GERCOR DREAM study

Final results from QUASAR2, a multicentre, international randomised phase III trial of capecitabine plus/minus bevacizumab in the adjuvant setting of stage II/III CRC

Dr Rachel Midgley of the University of Oxford, Oxford, UK reported that final results from the QUASAR2 study support data from two other trials suggesting no role for bevacizumab in the adjuvant CRC setting. The QUASAR2 biobank and linked database allows further collaborative biomarker hypotheses to be tested. According to QUASAR2 investigators there is a rationale for meta-analysis of all bevacizumab adjuvant CRC studies to more fully explore the putative temporal effect of bevacizumab administration on DFS.

The aims of QUASAR2 were to assess whether the addition of bevacizumab to single agent capecitabine increases DFS and OS in CRC patients after resection of the primary tumour; and to validate suggested, or discover new, biomarkers of bevacizumab efficacy and toxicity.

It was a phase III international randomised controlled trial, coordinated by the UK and recruiting in 6 countries. In addition to the collection of data on toxicity, DFS and OS, a biobank comprising 1350 FFPE blocks and 1000 germline DNA samples was established. Hypothesis-driven biomarkers, as MSI status, epithelial/stromal ratio, chromosomal instability, RAS, RAF, POLE and an 80-gene ion torrent panel, were analysed to assess their prognostic and predictive bevacizumab utility.

In total, 1941 patients were randomised in a 1:1 ratio and demographics and disease characteristics were well balanced between the two arms. The DFS in the whole trial population demonstrates that bevacizumab does not improve outcome in this setting (3-year DFS 75.4% for capecitabine/bevacizumab vs. 78.4% for capecitabine; HR 1.06; $p = 0.5$). Similarly OS was not improved (3-year OS 87.5% for capecitabine/bevacizumab vs. 89.4% for capecitabine; HR 1.11, $p = 0.3$). There may be a temporal trend in HRs (HRs: 1-year 0.83, 2-year 0.87, 3-year 1.32).

Subgroup analysis did not reveal a specific subpopulation (defined by stage/subsite/gender/age) that benefits from bevacizumab therapy.

Biomarker analyses confirm that high tumour stromal content confers a worse prognosis (3-year DFS HR 1.58; $p = 0.001$). However, there was no evidence this marker determined responsiveness to bevacizumab. MSS positivity was associated with a worse DFS in patients

treated with capecitabine/bevacizumab compared to those treated with capecitabine alone (in 840 patients HR 1.43; $p = 0.005$) suggesting a negative predictive effect for bevacizumab. For MSI positive patients, there was no significant difference in DFS between the two arms (in 135 patients HR 0.74; $p = 0.42$).

Dr Axel Grothey of the Mayo Clinic, Rochester, USA who discussed the study results, said that regarding the trial's design scientific validity, it was worth investigating given the clinical synergism between fluoropyrimidines and bevacizumab in the advanced CRC setting. However, omission of oxaliplatin for stage III cancers is of some concern. Sample size and statistical assumptions were adequate. The results are as expected with the exception of the MSI story. The MSI interaction might need preclinical studies. There is no need for confirmatory/additional studies. The results don't have implications for clinical practice, actually they confirm what we knew. In addition, the results don't have implications for future clinical trials, as well.

The unrestricted educational grant for this study was provided by F.Hoffmann-La Roche.

Reference

[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 \(CRC\)](#)

RELATED INFORMATION

[Click here to access the Conference abstracts.](#)

[Click here to access the meeting webcast page.](#)

Save the date

European Cancer Congress 2015 (ECC 2015), Vienna, Austria, 25-29 September 2015.

Affiliations and Disclosure

Affiliation

Dr Svetlana Jezdic, ESMO Head Office

Disclosure

No conflicts of interest to disclose.

Acknowledgment

ESMO would like to thank Drs Gligorov, von Minckwitz, Zhu, Kang, Lenz, Stintzing, Konecny, Krishnansu, Goss, Robert, McArthur, Weber, and Blay for giving their permission to publish images from the studies presented during the ESMO 2014 Congress in the ESMO Scientific report.

© Copyright 2014 European Society for Medical Oncology. All rights reserved worldwide.