Annals of Oncology Advance Access published February 27, 2014

Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM-study)

G. Folprecht[1], T. Gruenberger[2], W. Bechstein[3], H.-R. Raab[4], J. Weitz[5], F. Lordick[6], J. T. Hartmann[7], J. Stoehlmacher-Williams[1], H. Lang[8], T. Trarbach[9], T. Liersch[10], D. Ockert[11], D. Jaeger[12], U. Steger[13], T. Suedhoff[14], A. Rentsch[15], C.-H. Köhne[16]

[1]University Hospital Carl Gustav Carus, University Cancer Center / Medical Department I, Dresden, Germany

[2]Medical University of Vienna, Department of General Surgery, Vienna, Austria

[3]Goethe University, Department of Surgery, Frankfurt, Germany

[4]Klinikum Oldenburg, Department of Surgery, Oldenburg, Germany

[5]University Hospital Carl Gustav Carus, University Cancer Center / Department of Surgery, Dresden, Germany

[6]University Hospital Leipzig, University Cancer Center, Leipzig, Germany

[7]Christian-Albrechts-University, University Hospital, Medical Oncology, Kiel, Germany

[8]University Hospital Mainz, Department of Surgery, Mainz, Germany

[9]West German Cancer Center, Department of Medical Oncology, University Duisburg-Essen, Essen, Germany

[10]Georg-August-University, University Medical Center, Department of General and Visceral Surgery, Göttingen, Germany

[11]Krankenhaus der Barmherzigen Brüder, Department of Surgery, Trier, Germany

[12]University of Heidelberg, National Center for Tumor Diseases, Heidelberg, Germany

[13]University Hospital Würzburg, Department of Surgery, Würzburg, Germany

[14]Klinikum Passau, Medical Department II, Passau, Germany

[15]University Hospital Carl Gustav Carus, University Cancer Center / Biostatistics, Dresden, Germany

[16]Klinikum Oldenburg, Department of Oncology and Hematology, Oldenburg, Germany

Corresponding author: Dr. Gunnar Folprecht, University Cancer Center / Medical Dept. I, University Hospital Carl Gustav Carus, Fetscherstr. 74, 01307 Dresden, Germany, Tel: +49 351 458 4794, Gunnar.Folprecht@uniklinikum-dresden.de

Key Message: "Treatment in a multidisciplinary approach offers a relatively favorable 5-year survival of 45% in patients with initially unresectable colorectal liver metastases if they were resected following a conversion chemotherapy with cetuximab/FOLFOX or cetuximab/FOLFIRI, even if surgery was not curative in most patients. The median survival in all patients with liver limited disease was 35.7 months."

Keywords: colorectal cancer, liver metastases, cetuximab, chemotherapy, resection, multidisciplinary treatment.

Abstract

Background: Initially unresectable colorectal liver metastases can be resected after response to chemotherapy. While cetuximab has been shown to increase response and resection rates, the survival outcome for this conversion strategy needs further evaluation.

Patients and methods: Patients with technically unresectable and/or ≥5 liver metastases were treated with FOLFOX/cetuximab (arm A) or FOLFIRI/cetuximab (arm B) and evaluated with regard to resectability every 2 months. Tumour response and secondary resection data have been reported previously. A final analysis of overall survival (OS) and progression-free survival (PFS) was performed in December 2012.

Results: Between December 2004 and March 2008, 56 patients were randomised to arm A, 55 to arm B. The median OS was 35.7 [95% CI: 27.2-44.2] months (arm A: 35.8 [95% CI: 28.1- 43.6], arm B: 29.0 [95% CI: 16.0-41.9] months, HR 1.03 [95% CI: 0.66-1.61], *p=0.9)*. The median PFS was 10.8 [95% CI: 9.3-12.2] months (arm A: 11.2 [95% CI: 7.2-15.3], arm B: 10.5 [95% CI: 8.9-12.2] months, HR 1.18 [95% CI: 0.79-1.74], *p=0.4).* Patients who underwent R0 resection (*n=36*) achieved a better median OS (53.9 [95% CI: 35.9-71.9] months) than those who did not (21.9 [95% CI:17.1-26.7] months, *p<0.001).* The median disease-free survival for R0 resected patients was 9.9 [95% CI: 5.8-14.0] months, and the 5-year OS rate was 46.2 [95% CI: 29.5-62.9] %.

Conclusions: This study confirms a favourable long-term survival for patients with initially suboptimal or unresectable colorectal liver metastases who respond to conversion therapy and undergo secondary resection. Both FOLFOX/FOLFIRI plus cetuximab, appear to be appropriate regimens for "conversion" treatment in patients with *K-RAS* codon 12/13/61 wild-type tumours. Thus, liver surgery can be considered curative or alternatively as an additional "line of therapy" in those patients who are not cured.

Clinical trial number: NCT00153998, www.clinicaltrials.gov

Introduction

In recent years, the emergence of multidisciplinary treatment approaches, the availability of new antineoplastic drugs and the characterisation of molecular pathways have all contributed to an improvement in the therapy outcomes for patients with metastatic colorectal cancer. The finding that patients with initially unresectable liver metastases can become resectable after responding to chemotherapy and have a better long-term outcome than patients treated with chemotherapy alone [1] has led to the introduction of the concept of "conversion chemotherapy" into clinical practice.

The EGFR (epithelial growth factor receptor) antibody cetuximab improves both the overall survival (OS) and response rate when combined with first-line chemotherapy in patients whose tumours are without *K-RAS* mutations. [2,3] As a response to chemotherapy correlates with resection rate, [4] the improved efficacy shown by treatment regimens that included an EGFR antibody [5] made them of interest when investigating the concept of "conversion chemotherapy" in patients with colorectal liver metastases.

In the CELIM (***CE***tuximab in neoadjuvant treatment of unresectable colorectal ***LI***ver ***M***etastases) study, patients were randomised to receive either FOLFOX/cetuximab or FOLFIRI/cetuximab. We reported earlier a tumour response rate of 62% in all patients and 70% in patients with *K-RAS* codon 12/13/61 wild-type tumours. [6] The R0 resection rate for liver metastases was 34%, while the R0/1 resection and/or ablation rate was 46%. A surgical review of the computed tomography (CT) scans before and during treatment confirmed an improved resectability following treatment with chemotherapy plus cetuximab.[6]

In the current final analysis of this study, we report the long-term outcome for patients with initially unresectable colorectal liver metastases treated with chemotherapy plus cetuximab plus or minus secondary surgical resection of their metastases.

Methods

This open, multicentre randomised phase 2 trial studied either FOLFOX or FOLFIRI plus cetuximab in the treatment of patients with unresectable colorectal liver metastases. The primary endpoint was response rate. Secondary endpoints included resection rates, progression-free and overall survival, safety, and an assessment of predictive molecular markers of response and toxicity.

Patient selection

Patients with "unresectable" colorectal metastases confined to the liver were eligible for inclusion. "Unresectability" was defined, according to the categories used in the EORTC 40983 trial investigating resectable patients, [7] as patients with metastases that were viewed as technically unresectable by local evaluation on the basis of inadequate future liver remnant or sub-optimally resectable patients with ≥5 liver metastases. Patients fulfilling both of these inclusion criteria (≥5 metastases and technically unresectable) were grouped by the investigator to one of the two groups. Technical unresectability was defined as one of the following: infiltration of all liver veins, infiltration of the hepatic arteries or both portal vein branches. Enrolment was not limited to patients who were expected to become resectable after response to chemotherapy – patients with diffuse liver metastases were also eligible. In patients with synchronous liver metastases, the primary tumour had to be resected before study entry. Patients with a Karnofsky performance score of less than 80%, previous chemotherapy or EGFR-targeted therapy were excluded. Further details were described previously.[6]

Procedures

Patients were randomised to receive either FOLFOX/cetuximab (group A), or FOLFIRI/cetuximab (group B). Planned treatment was for eight cycles after which tumours were assessed for resectability by a multidisciplinary team as described previously.[6] Resection was offered to those patients whose liver disease had become resectable. Patients whose disease was still classed as unresectable continued on treatment until disease progression and were assessed for resectability every four cycles.

Patient tumours were evaluated retrospectively for *K-RAS* and *B-RAF* mutations. Furthermore, a group of surgeons performed a blinded review of the CT scans at baseline or after treatment. [6]

Statistical analysis

Overall survival and progression-free survival (PFS) were calculated from randomisation, and disease-free survival (DFS) from last resection within this protocol. The survival analysis was performed in December 2012 using the Kaplan-Meier estimation and Cox regression analysis.

A multivariate analysis for OS, PFS and DFS was performed with age (<65 vs. ≥65 years), sex, number of metastases at baseline (<5 vs. 5-10 vs. >10), inclusion due to technically resectability or ≥5 metastases, resectability according to imaging review, treatment arm, *K-RAS* status, synchronous vs. metachronous metastases, CEA (≤5, 5-50, >50 ng/ml), and white blood count (continuous variable). For OS and PFS, it was repeated with the post-treatment variables of resection (no resection vs. resection and/or radiofrequency ablation), tumour response (confirmed partial response/complete response vs. stable disease/progressive disease) and imaging review after treatment.

The sample size calculation, the definition of the primary endpoints and the detailed analysis of the surgical review were reported previously. [6]

Ethics

All patients provided written informed consent. The study was approved by the health authorities and the local ethics committees.

Results

Patient population

Between December 2004 and March 2008, patients were randomised to receive either FOLFOX/cetuximab (group A, *n=56*) or FOLFIRI/cetuximab (group B, *n=55*) in 16 centres in Germany and one in Austria. Two patients in group A did not start study treatment due to withdrawal of con-

sent or extrahepatic disease (retrospectively detected on pre-randomisation imaging). One patient in each group discontinued treatment before the first dose was fully completed. One patient in group B was not evaluable for response due to their early death from pulmonary embolism (Figure 1).

The patients' characteristics were reported earlier. [6] In summary, 70 patients had *K*-RAS codon 12/13/61 wild-type tumours, 29 patients had tumours with *K-RAS* mutations and 12 patients had tumours of unknown *K-RAS* mutational status. Three patients had tumours with a *B-RAF* mutation. Thirty patients (27%) had <5 liver metastases, 58 patients (52%) had 5-10 liver metastases, and 19 patients >10 liver metastases (17%; unknown number in four patients). Fourteen patients had had previous liver surgery.

Survival according to treatment arms

The median OS (all patients) was 35.7 [95% CI: 27.2-44.2] months and the median PFS was 10.8 [95% CI: 9.3-12.2] months (Figure 2 A). The estimated 3- and 5-year OSs were 48.3% [95% CI: 38.9-57.7%] and 27.5% [95% CI: 18.7-36.3%], respectively, with an estimated PFS rate at 3 years of 5.7% [95% CI: 1.4-10.0%].

There were no statistically significant differences regarding the outcome according to treatment group. The median OS was 35.8 months [95% CI: 28.1-43.6] in arm A and 29.0 months [95% CI: 16.0-41.9] in arm B, HR 1.03 [95% CI: 0.66-1.61], *p=0.9*. The median PFS was 11.2 [95% CI: 7.2-15.3] and 10.5 [95% CI: 8.9-12.2] months for arms A and B, respectively (HR 1.18 [95% CI: 0.79-1.74], *p=0.4*, Figure 2 B).

Patients with *K-RAS* wild-type tumours showed a non-significant trend towards a longer PFS (11.9 [95% CI: 8.2-15.6] vs. 9.9 [95% CI: 4.5-15.2] months) and OS (36.6 [95% CI: 25.3-47.8] vs. 27.4 [95% CI: 15.7-39.1] months) compared with those with *K-RAS* mutant tumours. The hazard ratios for PFS and OS were 1.29 [95% CI: 0.82-2.04] and 1.41 [95% CI: 0.84-2.34], respectively (Figure 2C). The power of this explorative analysis is however limited due to the low number of patients with *K-RAS* mutant tumours. As for the ITT cohort, there was no detectable difference between the treatment groups in

the subgroup of patients with *K-RAS* wild-type tumours. The OS was 36.1 [95% CI: 21.1-51.1] and 41.6 [95% CI: 22.6-60.6] months for treatment arms A and B, and the PFS was 12.1 [95% CI: 5.2-19.1] and 11.5 [95% CI: 8.8-14.1] months (Figure 2D). The hazard ratios for OS and PFS in s *K-RAS* wild-type tumour patients were 0.86 [95% CI: 0.48-1.53] and 1.13 [95% CI: 0.69-1.85], respectively.

Survival, response and resectability

Patients who had undergone an R0 resection had a significantly longer OS (median: 53.9 [95% CI: 35.9-71.9] months) than patients without any resection (21.9 [95% CI: 17.1-26.7] months, HR 0.29 [95% CI: 0.17-0.50], *p<0.001*). The median PFS was 15.4 [95% CI: 11.4-19.5] months in patients who had undergone an R0 resection and 6.9 [95% CI: 5.9-8.0] months in patients who had not undergone a secondary resection for their disease, (HR 0.31 [95% CI: 0.19-0.50], *p<0.001*). Patients with macroscopically complete resections (non-R0) or those who had undergone radiofrequency ablation with or without additional resection had a similar survival outcome to those R0 resected patients (Figure 3A). The 5-year survival rate for R0 resected patients was 46.2% [95% CI: 29.5-62.9%].

The median DFS for the 36 patients who had undergone R0 resection was 9.9 [95% CI: 5.8-14.0] months. Three patients (8%) remained disease free at three years. The number of metastases at baseline had a significant influence on the DFS time (Figure 3B, *p<0.001*).

Resections following response to chemotherapy, and tumour response itself had a major influence on the OS (Figure 4A). To explore the additional influence of liver resection in patients with a major response, a subgroup analysis for OS was performed in patients who had achieved either a partial or complete response. Figure 4B demonstrates the prognostic influence of liver resection in this patient subgroup (patients with R0 resection vs. patients without resection: HR 0.42 [95% CI: 0.21-0.86], *p=0.021*).

We also analysed whether resectability determined during the retrospective imaging review was prognostic for survival. Interestingly, resectability determined on the scans after chemotherapy but not at baseline was predictive for the OS in the univariate analysis (Figures S1A and S1B, only-online

supplementary material) emphasising the value of conversion chemotherapy. The results of the multivariate analysis are presented in the supplementary table S1..

Discussion

Only a few years ago, the patients included in this study would have been regarded as incurable. Thus, in this context, the 5-year OS rate of ~45% in R0 resected patients is perhaps the most important result of this trial, and confirms in a multicentre study the value of intensive "conversion chemotherapy" together with liver surgery managed within a multidisciplinary environment. Both regimens in the present study achieved high response and resection rates. Of those patients not considered to be resectable prior to study treatment, 34% finally underwent R0 resection, and an additional 12% underwent R1 resection and/or radiofrequency ablation. [6] There is probably - except for sufficient postoperatively remaining functional liver tissue – no generally accepted definition of unresectability. In particular, there is uncertainty about which patients should be regarded as "oncologically unresectable" and in terms of treatment decision making about those patients who need technically demanding surgery but have an unfavourable prognosis. In the present study, we used the pragmatic definition of unresectability used for the EORTC 40983 study in patients with resectable liver metastases. Thus, our patients had either technically unresectable and/or ≥5 metastases. In situations where patients fulfilled both inclusion criteria they were assigned by the investigator into one of the two groups. However, due to the lack of a clear definition of resectability/unresectability it can never be excluded in the clinical practice setting, that patients regarded as unresectable in one centre might be considered to be resectable in another centre. The likelihood of a major discrepancy was 7% according to the blinded surgical review based on imaging information. [6] Interestingly, patients enrolled into the trial because they had ≥5 metastases (and not due to technically unresectable metastases) had a worse DFS according to the multivariate analysis emphasising that resectability should be defined by both technical and prognostic factors. Interestingly, according to the retrospective imaging review post-treatment resectability but not initial resectability was associated with a better OS, confirming the importance of conversion chemotherapy (Figure S1, online-only).

We are unable to conclude from the present trial to what extent cetuximab contributed to these favourable results, because all patients received EGFR antibody therapy. However, increased response rates and higher resection rates in patients with *K-RAS* wild-type tumours who received cetuximab plus FOLFIRI or FOLFOX versus chemotherapy alone were reported in both the CRYSTAL and OPUS studies which enrolled patients with both liver-limited and non-liver-limited metastatic colorectal cancer, [2,3] and confirmed in a recently published randomised trial conducted in patients with unresectable, liver-limited, colorectal metastases. [8]

No statistically significant difference was detected between the combinations of FOLFOX/cetuximab and FOLFIRI/cetuximab in terms of efficacy. Although the statistical power is limited due to the sample size, this finding is interesting for the interpretation of the results of the COIN and NORDIC VII trials [9,10] and suggests that the negative results of these two trials may not be attributable to combinations of cetuximab/oxaliplatin but to other factors, such as the different fluoropyrimidine schedules. Recent findings have indicated that EGFR antibody therapy is ineffective in patients whose tumours carry *K-RAS* mutations beyond the most frequently tested exon 2 codon12/13 mutations and also in patients with *N-ras* mutated tumours. [11] In this trial, patients had been tested for *K-RAS* mutations in codon 12, 13 (exon 2), codon 61 and *B-RAF*. The low frequency of further mutations is unlikely to change the study results.

Thus, long OS was achieved although only a few patients remained free of disease progression at 3 years. Although repeated resections of recurrent metastases might have cured additional patients, [12] surgery itself was not curative in the majority of patients. This finding is consistent with the findings of other studies of liver resection in initially unresectable patients. [13] [14]

Given the relative safety when used in experienced hands and the complete “remission” achieved by liver surgery, such surgery, although often not curative, seems to make an important contribution to the overall continuum of care of the patients in our study and may reduce cell clones not sensitive to a given chemotherapy. Compared with the time to re-introduction (median 3-4 months) of chemotherapy following discontinuation of therapy in trials investigating stop-and-go strategies, [15,16] the

median DFS of 9.9 months for R0 resected patients in the present trial compares favourably, even if there was no durable cure, and represents a “further line of palliative treatment”. This effect might be overestimated as all resected patients had a response to chemotherapy and therefore represent a better prognostic group. However, the beneficial effect of surgery can still be identified in the subset of patients who responded to chemotherapy (Figure 4B). These findings may provide a useful basis from which to discuss and manage patients’ realistic expectations regarding the outcomes of a multidisciplinary team approach to their treatment. Recent results have shown that patients with metastatic colorectal cancer usually overestimate their probability of being cured [17] and their survival,[18] following chemotherapy.

Early recurrence within the first 6 months after resection was observed in nearly one third of the patients. A short disease-free interval was associated with a high number of liver metastases (>10) (Figure 3B), synchronous metastases, and a high CEA level prior to treatment – factors well known to be associated with poor OS. [19,20] Whether surgery improves OS in patients with a very high risk of recurrence and how this group can be best defined remains uncertain. Trials evaluating this question may be of value.

In conclusion, the CELIM study has demonstrated a favourable outcome for patients with liver-limited disease in a multicentre setting using a multidisciplinary treatment approach involving an effective systemic treatment followed by resection of their colorectal liver metastases, whenever possible. Whether the treatment can be improved by more intensive conversion therapy combinations, for example FOLFOXIRI/cetuximab [21] instead of FOLFIRI/cetuximab or FOLFOXIRI/bevacizumab [22] instead of FOLFOXIRI is subject of current clinical trials (NCT01802645).

Acknowledgement

We thank all patients and their relatives for their willingness to participate in the trial, and the study teams at the University Hospitals in Vienna (Austria), Tübingen, Göttingen, Munich (Rechts der Isar), Heidelberg, Frankfurt, Essen, Mannheim, Würzburg Dresden, at the Klinikum Passau, Celle, Magdeburg, Oldenburg, Aschersleben, and at the Krankenhaus der Barmherzigen Brüder Trier for their enthusiastic work, Ute Schubert for her great assistance in data collection, and Merck KGaA, Pfizer and Sanofi-Aventis for the financial support.

Funding

The study was designed by GF and CHK, who developed the protocol, and was supported by educational grants from Merck KGaA, Pfizer and Sanofi-Aventis (grant numbers: NA). The legal sponsor of the study was the Corporation of Knowledge and Technology Transfer at the Technical University of Dresden (GWT-TUD GmbH), which was responsible for data collection, the database, and statistical analysis. GF and C-HK had full access to all data. GF had the final responsibility for the submission of the manuscript for publication. The financial sponsors had no role in the collection, analysis, or interpretation of data, or the writing of the report.

Disclosures

GF / CHK received a study grant for this trial (Merck KGaA, Pfizer and Sanofi-Aventis). GF received further study grants (Merck KGaA, Pfizer), honoraria for advisory boards (Merck KGaA, Roche/Genentech, Bristol-Myers-Squibb, Sanofi-Aventis), and lecture honoraria (Merck KGaA, Roche/Genentech, Sanofi-Aventis, Novartis). TG received study grants (Merck KGaA, Roche/Genentech, Sanofi-Aventis), honoraria for advisory boards (Merck KGaA, Roche/Genentech), and lecture honoraria (Merck KGaA, Roche/Genentech, Amgen). FL received honoraria (Merck KGaA, Amgen, Sanofi-Aventis) and research funding (Merck KGaA, Sanofi-Aventis). TT received study grants, honoraria for advisory boards and lectures honoraria from Merck KGaA. JSW received honoraria for advisory boards and lectures honoraria from Merck KGaA. JTH received honoraria for advisory boards,

lecture honoraria and research funding (all Merck KGaA). CHK received study grants (Merck KGaA, Pfizer), honoraria for advisory boards (Merck KGaA, Bristol-Myers-Squibb, Bayer), and lecture honoraria (Merck KGaA, Roche/Genentech, Sanofi-Aventis, Novartis). WB, HRR, JW, HL, TL, DO, DJ, US, TS, AR declare to have no potential conflicts of interest.

Figures and Tables

Figures

Supplementary material

References

1. Morris EJ, Forman D, Thomas JD et al. Surgical management and outcomes of colorectal cancer liver metastases. Br J Surg 2010; 97: 1110-8.

2. Van Cutsem E, Köhne CH, Lang I et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011; 29: 2011-9.

3. Bokemeyer C, Bondarenko I, Hartmann JT et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann Oncol 2011; 22: 1535-46.

4. Folprecht G, Grothey A, Alberts S et al. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. Ann Oncol 2005; 16: 1311-9.

5. Folprecht G, Lutz M, Schöffski P et al. Cetuximab and irinotecan/5-fluorouracil/folinic acid is a safe combination for the first-line treatment of patients with epidermal growth factor receptor expressing metastatic colorectal carcinoma. Ann Oncol 2006; 17: 450-6.

6. Folprecht G, Gruenberger T, Bechstein WO et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 2010; 11: 38-47.

7. Nordlinger B, Sorbye H, Glimelius B et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008; 371: 1007-16.

8. Ye LC, Liu TS, Ren L et al. Randomized Controlled Trial of Cetuximab Plus Chemotherapy for Patients With KRAS Wild-Type Unresectable Colorectal Liver-Limited Metastases. J Clin Oncol 2013; 31: 1931-8.

9. Maughan TS, Adams RA, Smith CG et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet 2011; 377: 2103-14.

10. Tveit KM, Guren T, Glimelius B et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. J Clin Oncol 2012; 30: 1755-62.

11. Douillard JY, Oliner KS, Siena S et al. Panitumumab FOLFOX4 Treatment and RAS Mutations in Colorectal Cancer. N Engl J Med 2013; 369: 1023-34.

12. Lam VW, Pang T, Laurence JM et al. A systematic review of repeat hepatectomy for recurrent colorectal liver metastases. J Gastrointest Surg 2013; 17: 1312-21.

13. Alberts SR, Horvath WL, Sternfeld WC et al. Oxaliplatin, Fluorouracil, and Leucovorin for Patients With Unresectable Liver-Only Metastases From Colorectal Cancer: A North Central Cancer Treatment Group Phase II Study. J Clin Oncol 2005; 23: 9243-9.

14. Adam R, Wicherts DA, de Haas RJ et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? J Clin Oncol 2009; 27: 1829-35.

15. Chibaudel B, Maindrault-Goebel F, Lledo G et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. J Clin Oncol 2009; 27: 5727-33.

16. Adams RA, Meade AM, Seymour MT et al. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first-line treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet Oncol 2011; 12: 642-53.

17. Weeks JC, Catalano PJ, Cronin A et al. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med 2012; 367: 1616-25.

18. Mende M, Trautmann K, Rentsch A et al. Patients' perspectives on palliative chemotherapy of colorectal and non - colorectal cancer: a prospective study in a chemotherapy- experienced population. BMC Cancer 2013; 13: 66.

19. Rees M, Tekkis PP, Welsh FK et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg 2008; 247: 125-35.

20. Spelt L, Andersson B, Nilsson J et al. Prognostic models for outcome following liver resection for colorectal cancer metastases: A systematic review. Eur J Surg Oncol 2012; 38: 16-24.

21. Folprecht G, Schuette K, Stoehlmacher J et al. Cetuximab and FOLFOXIRI: Dose-escalation study in previously untreated patients with metastatic colorectal cancer. Proc Gastrointest Canc Symp (ASCO/AGA/ASTRO/SSO) , abstract 480. 2010.

22. Falcone A, Cremolini C, Masi G et al. FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group. J Clin Oncol (Meeting Abstracts) 2013; 31: 3505.

Figure 1: CONSORT diagram

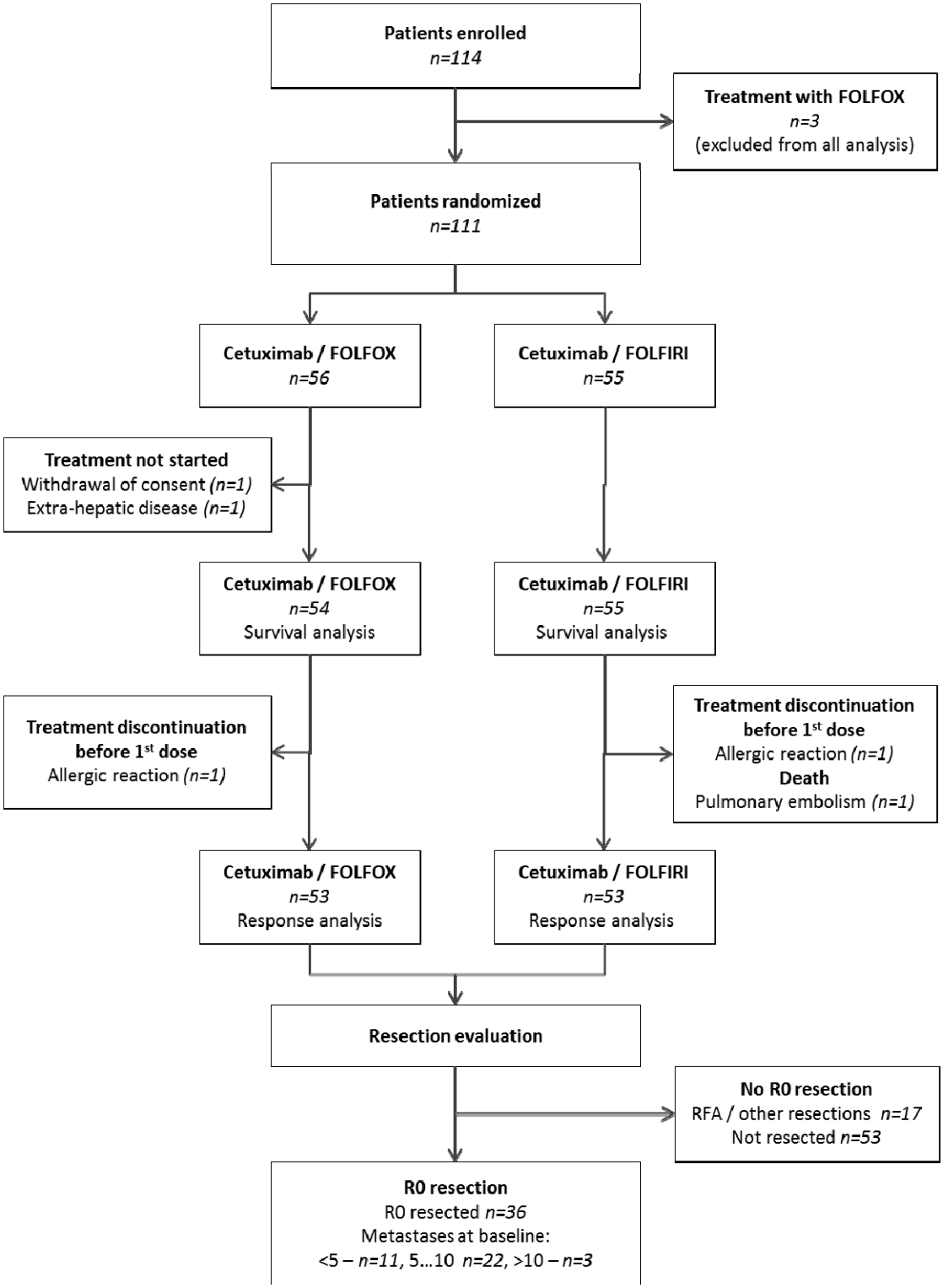
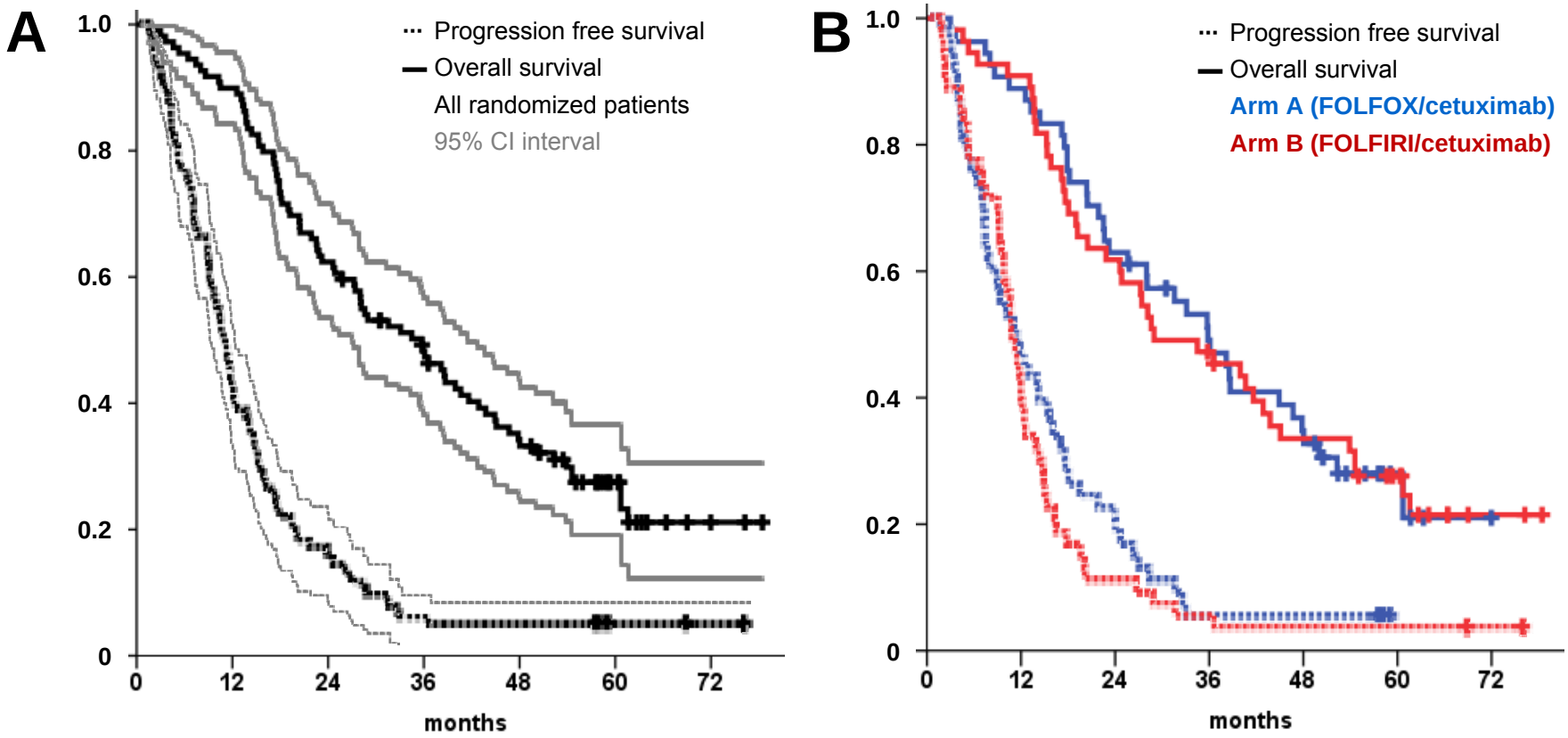
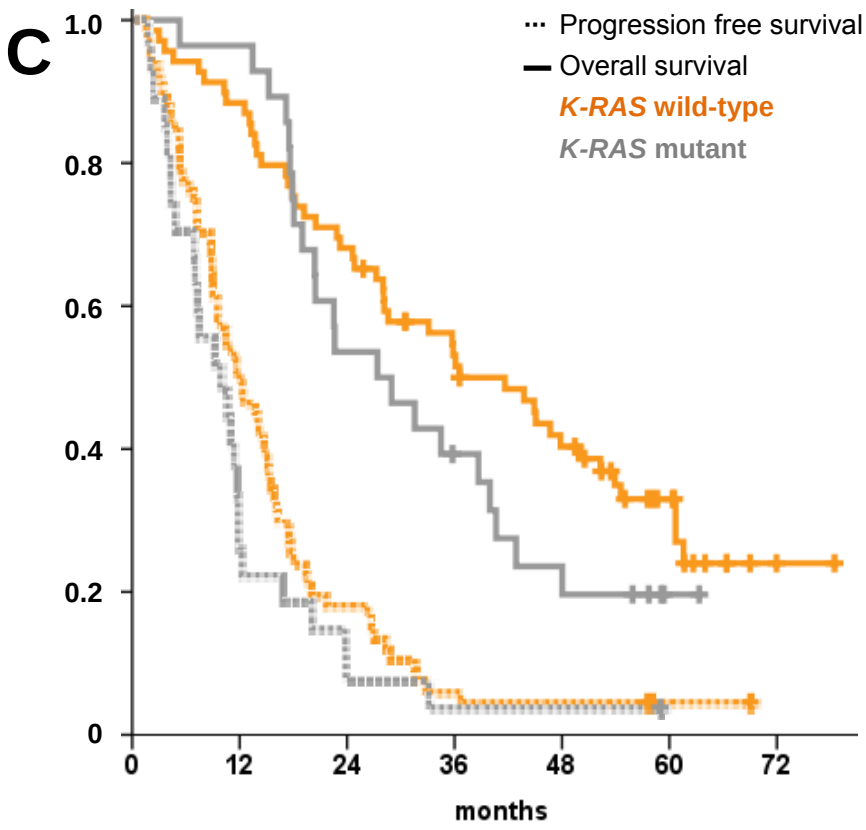


Figure 2: Progression-free and overall survival according to treatment

(A) Progression free survival and overall survival in all randomised patients, (B) according to treatment arm (arm A- blue, arm B – red), (C) according to *K-RAS* status (*K-RAS* wild-type orange, *K*-RAS mutant – grey), (D) in the *K-RAS* wild-type subgroup according to treatment arm (arm A- blue, arm B – red). The differences between treatment groups and according to K-RAS mutational status are not significant.





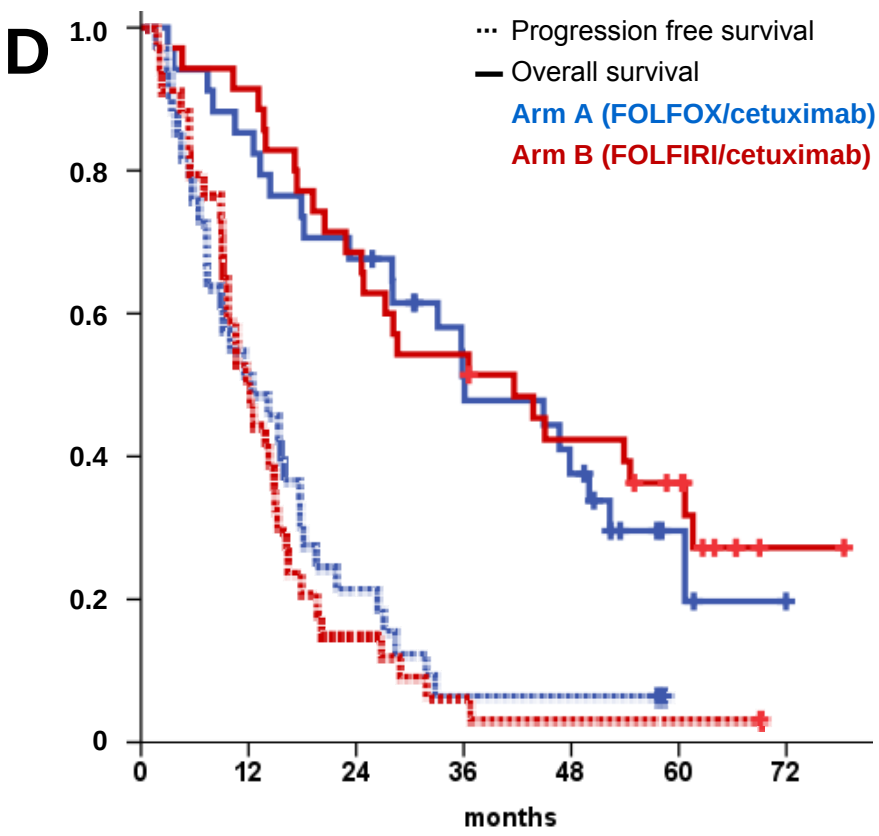


Figure 3: Survival according to resection

A Progression free survival (dotted lines) and overall survival (solid) lines from randomisation in patients with R0 resection (green), R1 resection or radiofrequency ablation with or without R0/1 resection (yellow) and without resection (red).

B Disease free survival *from resection* in patients with R0 resection in all patients (black), and according to the number of metastases at baseline (< 5 metastases – green, 5-10 metastases – yellow, > 10 metastases – red).

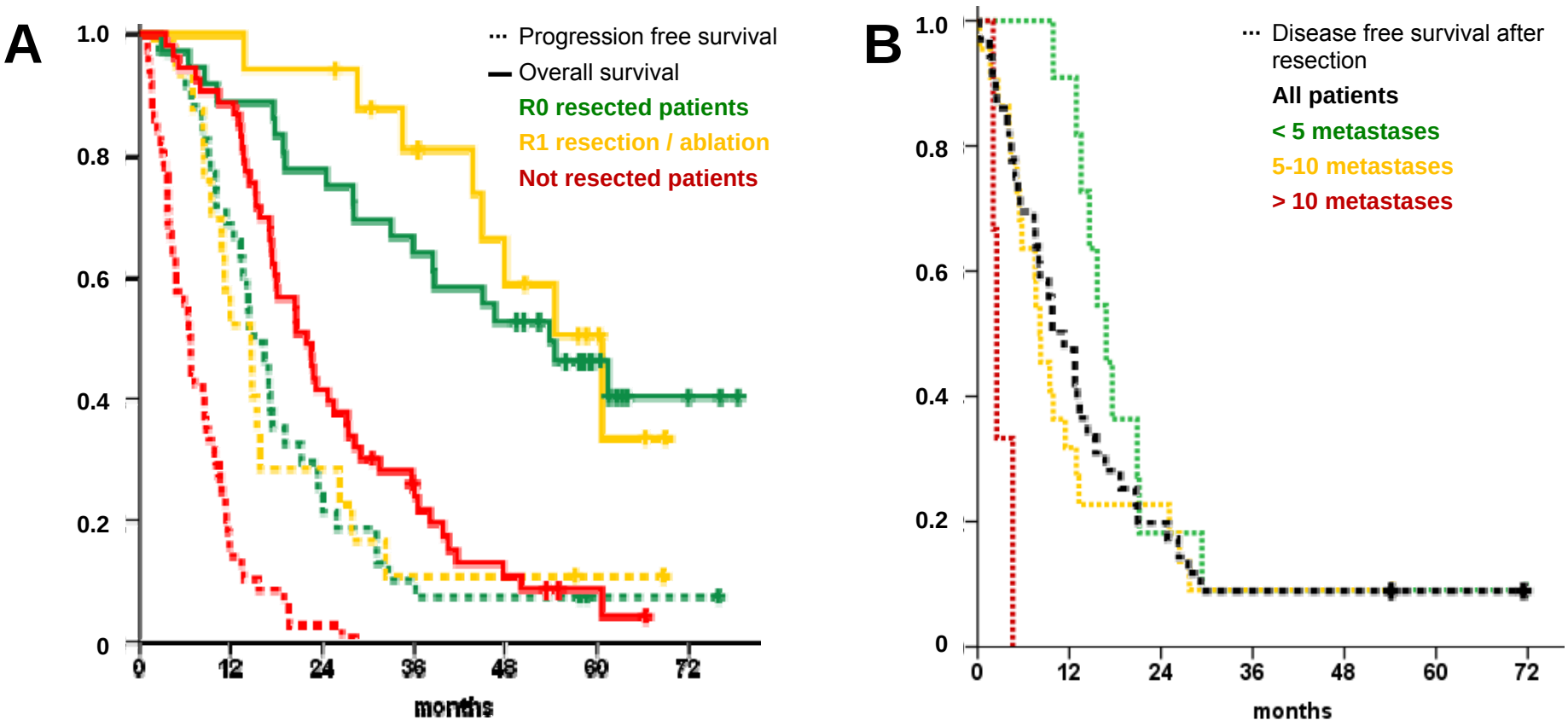


Figure 4: Overall survival according to tumour response and resection

A Overall survival according to tumour response, patients with partial remission (PR) and complete remission (CR) – green, patients with stable disease (SD) and progressive disease (PD) – orange

B Overall survival in patients who achieved a PR or CR according to resectional status (R0 resection - green, R1 resection or radiofrequency ablation with or without R0/1 resection – yellow, and patients without resection red)