Evaluation of prognostic factors in liver-limited metastatic colorectal cancer: a preplanned analysis of the FIRE-1 trial

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Background: Liver-limited disease (LLD) denotes a specific subgroup of metastatic colorectal cancer (mCRC) patients.

Patients and Methods: A total of 479 patients with unresectable mCRC from an irinotecan-based randomised phase III trial were evaluated. Patients with LLD and non-LLD and hepatic resection were differentiated. Based on baseline patient characteristic, prognostic factors for hepatic resection were evaluated. Furthermore, prognostic factors for median overall survival (OS) were estimated via Cox regression in LLD patients.

Results: Secondary liver resection was performed in 38 out of 479 patients (resection rate: 7.9%). Prognostic factors for hepatic resection were LLD, lactate dehydrogenase (LDH), node-negative primary, alkaline phosphatase (AP) and Karnofsky performance status (PS). Median OS was significantly increased after hepatic resection (48 months), whereas OS in LLD (17 months) and non-LLD (19 months) was comparable in non-resected patients. With the inapplicability of Koehne’s risk classification in LLD patients, a new score based on only the independent prognostic factors LDH and white blood cell (WBC) provided markedly improved information on the outcome.

Conclusion: Patients undergoing hepatic resection showed favourable long-term survival, whereas non-resected LLD patients and non-LLD patients did not differ with regard to progression-free survival and OS. The LDH levels and WBC count were confirmed as prognostic factors and provide a useful and simple score for OS-related risk stratification also in LLD.

Rejection of hepatic and/or pulmonary metastases from colorectal cancer remains the only curative option in stage IV patients, but only 10–20% of patients can be considered for primary resection at the time of diagnosis of metastatic disease. (Adam et al, 2010) With the availability of active chemotherapy regimens, patients initially considered unresectable may be converted into resectable patients and possible long-time survivors. Numerous trials have reported favourable long-time survival and 5-year survival rates ~ 40% in these patients (Adam et al, 2001; Kopetz et al, 2009).

For patients with initially unresectable metastatic disease, the optimal conversion chemotherapy regimen remains uncertain to this date (Schmoll et al, 2012). Different combination chemotherapy regimens along with monoclonal antibodies have been investigated to induce downsizing and to achieve secondary resectability (Alberts et al, 2005; Barone et al, 2007; Folprecht et al, 2010; Power and Kemeny, 2011; Bruera et al, 2012; Petrelli and Barni, 2012). Relating to this, patients with liver-limited disease (LLD) who are considered unresectable at the time of...
Patients. The FIRE-1 trial was conducted in the treatment era without the use of targeted therapy comparing first-line chemotherapy with either FU/FIRI or mIROX in a German multicentre phase III trial (Fischer von Weikersthal et al., 2010). In the standard arm, FU/FIRI consisted of irinotecan 80 mg m\(^{-2}\) as a 0.5-h infusion followed by folinic acid 500 mg m\(^{-2}\) applied over 2 h and 5-fluorouracil 2000 mg m\(^{-2}\) given as a 24-h infusion weekly six times. In the experimental mIROX arm, patients received irinotecan 80 mg m\(^{-2}\) as a 0.5-h infusion weekly six times plus oxaliplatin 85 mg m\(^{-2}\) as 2-h infusion on days 15 and 29 of each cycle. In both arms, treatment was repeated every 49 days.

Patients between 18 and 75 years were eligible if they had histologically proven metastatic adenocarcinoma of the colon or rectum without prior chemotherapy for metastatic disease. Patients with resectable metastatic disease were not included in this trial. Prior adjuvant chemotherapy was allowed with a treatment-free interval ≥ 6 months and did not include topoisomerase I inhibitors or platinum compounds. A Karnofsky performance status (KPS) ≥ 70% (i.e. ECOG 0–1), adequate liver and bone marrow function parameters and bidimensionally measurable tumour lesions were mandatory. Written informed consent was obtained from each patient. Patients were excluded if they had symptoms of peritoneal carcinomatosis or brain metastasis. Fisher’s exact test and the χ\(^2\)-test was applied to compare patients’ characteristics and subgroup analyses. Using the Kaplan–Meier estimator, PFS and OS were estimated.

RESULTS

Patient population. Between July 2000 and October 2004, 495 patients from 48 German centres were enrolled. Sixteen patients were considered ineligible because of protocol violation (hyperbilirubinemia, n = 1) or documentation failure (n = 15). A total of 479 patients were randomly assigned to receive either the FU/FIRI (n = 238) or the mIROX (n = 241) regimen. Overall, the treatment arms were well balanced with regard to stratification factors KPS, LDH and adjuvant treatment, and other patient or tumour characteristics. (Fischer von Weikersthal et al., 2010) After the present survival update, the median follow-up time was 55.4 months (95% confidence interval, 50.0–60.7 months) with an event rate of 87.1% for overall survival.

Patient characteristics. Baseline parameters and clinical characteristics of patients with LLD (with or without resection of metastases) and non-LLD are shown in Table 1. Although sex was well balanced between the subgroups, patients with LLD tended to be younger than resected patients and non-LLD patients (median age 61.8, 62.7 and 63.5 years, P = 0.131). Performance status was significantly better in resected patients (KPS 100% in...
| Table 1. Baseline characteristics |
|----------------------------------|
| **Hepatic resection, n = 38 | LLD, n = 215 | Non-LLD, n = 226 |
| **n | % | n | % | n | % | P-value |
| **Sex** |
| Male | 26 | 68.4 | 151 | 70.2 | 158 | 69.9 | 0.975 |
| Female | 12 | 31.6 | 64 | 29.8 | 68 | 30.1 |
| **Age at randomisation** |
| Median (years) | 62.7 | 61.8 | 63.5 | 0.131 |
| Range | 32–73 | 32–78 | 22–79 |
| **Karnofsky performance status** |
| 100% | 24 | 63.2 | 76 | 35.3 | 90 | 39.8 | <0.001 |
| 70–90% | 14 | 36.8 | 139 | 64.7 | 136 | 60.2 |
| **Localization of primary** |
| Colon | 23 | 60.5 | 136 | 63.3 | 128 | 56.6 | 0.365 |
| Rectal | 15 | 39.5 | 79 | 36.7 | 98 | 43.4 |
| **T-stage of primary** |
| T1/T2 | 5 | 13.2 | 15 | 7.0 | 23 | 10.2 | 0.101 |
| T3/T4 | 33 | 86.8 | 190 | 88.4 | 186 | 82.3 |
| NA | — | — | 10 | 4.6 | 17 | 7.5 |
| **N-stage of primary** |
| Nodal negative | 15 | 39.5 | 37 | 17.2 | 70 | 31.0 | <0.001 |
| Nodal positive | 23 | 60.5 | 165 | 76.7 | 130 | 57.5 |
| NA | — | — | 13 | 6.0 | 26 | 11.5 |
| **Resection of primary** |
| No | 2 | 5.3 | 11 | 5.1 | 16 | 7.1 | 0.673 |
| Yes | 36 | 94.7 | 204 | 94.9 | 210 | 92.9 |
| **Development of metastasis** |
| Synchronous | 29 | 76.3 | 159 | 74.0 | 102 | 45.1 | <0.001 |
| Metachronous | 9 | 23.7 | 56 | 26.0 | 124 | 54.9 |
| **Localization of metastasis** |
| Liver | 38 | 100.0 | 215 | 100.0 | 150 | 68.5 | <0.001 |
| Liver only | 36 | 94.7 | 215 | 100.0 | — | — | <0.001 |
| Lung | 2 | 5.3 | — | — | 123 | 56.2 | <0.001 |
| Lymph node | 2 | 5.3 | — | — | 74 | 33.8 | <0.001 |
| Peritoneal | — | — | — | — | 15 | 6.8 | <0.001 |
| Other | — | — | — | — | 13 | 5.9 | <0.001 |
| **No. of metastatic sites** |
| 1 | 36 | 94.7 | 215 | 100.0 | 40 | 17.7 | <0.001 |
| ≥2 | 2 | 5.3 | — | — | 186 | 82.3 |
| **CEA level at baseline** |
| <200 ng ml\(^{-1}\) | 32 | 84.2 | 132 | 61.4 | 146 | 64.6 | 0.108 |
| >200 ng ml\(^{-1}\) | 5 | 13.2 | 57 | 26.5 | 47 | 20.8 |
| NA | 1 | 2.6 | 26 | 12.1 | 33 | 14.6 |
| **Alkaline phosphatase** |
| ≤300 U l\(^{-1}\) | 28 | 73.7 | 93 | 43.3 | 112 | 49.6 | <0.001 |
| >300 U l\(^{-1}\) | 9 | 23.7 | 107 | 49.8 | 91 | 40.3 |
| NA | 1 | 2.6 | 15 | 7.0 | 23 | 10.2 |
| **LDH** |
| ≤250 U l\(^{-1}\) | 32 | 84.2 | 107 | 49.8 | 131 | 58.0 | <0.001 |
| >250 U l\(^{-1}\) | 6 | 15.8 | 106 | 49.3 | 89 | 39.4 |
| NA | — | — | 2 | 0.9 | 6 | 2.6 |
63.2% of the patients) than in LLD- (35.2%) or non-LLD patients (39.8%) \((P<0.001)\). Tumour characteristics of the primary were comparable regarding T-stage. Node-positive tumours were documented in 61% of resected patients, 77% of LLD patients and 58% of non-LLD patients \((P<0.001)\). Resection of primary tumour was performed in 94.7% in resected patients and 94.9% of LLD- and 92.9% of non-LLD patients, respectively. Around 75% of resected and LLD patients developed their metastases within 6 months of first diagnosis \((\text{synchronous})\), compared with only 45% of non-LLD patients. Localisation of metastases consequently differed among the three groups with 95% of resected patients suffering from LLD. In non-LLD patients, liver was the most common localisation \((69\%)\), followed by lung \((57\%)\), lymph node \((34\%)\) and peritoneal carcinomatosis \((7\%)\). Relating to this, the number of metastatic sites was \(\geq2\) in 82% of non-LLD patients, whereas only 5% of resected patients had hepatic lesions. The levels of AP were significantly lower \((\leq8000\text{per}\mu\text{l})\) in patients who underwent hepatic resection \((73.7\%)\) compared with LLD patients \((43.3\%)\) and non-LLD patients \((49.6\%)\) \((P<0.001)\). Elevated baseline LDH levels were observed in 49% of LLD patients and 39% of non-LLD patients, whereas only 16% of resected patients had LDH levels > 250 U/L \((P<0.001)\). In patients who underwent hepatic resection, WBC count was elevated \((\geq8000\text{per}\mu\text{l})\) in 32% compared with 45% of LLD patients and 41% of non-LLD patients \((P<0.001)\). According to Koehne et al (Kohne et al, 2002), a score based on PS, AP level, number of metastatic sites and WBC count allows the differentiation of three prognostic groups: low, intermediate and high risk. In patients with hepatic resection, 82% were classified 'low risk' compared with 99% of LLD patients. In non-LLD patients, only 23% were classified as 'low risk', 55% as 'intermediate risk' and 14% as 'high risk' \((P<0.001)\). First-line chemotherapy with FUFIIRI as opposed to mIROX was more common in patients who achieved resectability \((60.5\%)\) compared with 57% of LLD patients and 47% of non-LLD patients \((P=0.045)\).

**Best response according to subgroups.** To explore the effect of conversion chemotherapy in unresectable mCRC, best response according to patients who underwent hepatic resection (LLD), LLD and non-LLD patients is summarised in Table 2. Complete response was observed in 15.2% of resected patients, 8.4% of LLD and 6.2% of non-LLD patients. More than 60% of resected patients could achieve a partial response, compared with only 32.6% of LLD patients \((P=0.002)\). The rate of partial response in non-LLD patients was comparable to LLD patients \((36.3\%\); \(P=0.446)\). A total of 10 patients \((24.2\%)\) could achieve secondary hepatic resection with stable disease \((SD)\) at best response. Comparable stable disease rates were also achieved by LLD and non-LLD patients \((31.6\%\) and 36.3\%). Progressive disease was present in 14.9% of LLD and 10.6% of non-LLD patients \((P=0.422)\). Response evaluation was not possible in a total of 68 patients.

**Progression-free survival and overall survival according to subgroups.** Patients who underwent secondary hepatic resection, showed prolonged PFS \((16.6\text{ months})\) and OS \((48.0\text{ months})\), which were significantly \((P<0.001)\) longer than in not-resected groups. Both not-resected patient groups, LLD- and non-LLD, had a shorter PFS \((6.5\text{ months vs }8.2\text{ months})\) and OS \((17.0\text{ months vs }19.0\text{ months})\). (Table 3; Figure 1A and B).

**Prognostic factors for hepatic resection.** To evaluate prognostic factors for secondary hepatic resection, the following baseline parameters were analysed: age, sex, KPS, localisation of primary tumour, T-stage of primary, N-stage of primary, resection of primary, development of metastases, localization of metastases, number of metastatic sites, adjuvant treatment, AP level, LDH levels, WBC count and treatment arm. In a multivariate logistic

### Table 1. (Continued)

| Treatment | Hepatic resection, \(n=38\) | LLD, \(n=215\) | Non-LLD, \(n=226\) |
|-----------|----------------|----------------|----------------|
|           | \(n\) | % | \(n\) | % | \(n\) | % | \(P\)-value |
| WBC       |             |             |             |             |             |             |             |
| <8000 per \(\mu\text{l}\) | 26 | 68.4 | 115 | 53.5 | 130 | 57.5 | 0.224 |
| \(\geq8000\text{per}\mu\text{l}\) | 12 | 31.6 | 96 | 44.7 | 88 | 40.9 |             |
| NA        | - | - | 4 | 1.9 | 8 | 3.6 |             |
| Haemoglobin |             |             |             |             |             |             |             |
| \(<10\text{ g dl}^{-1}\) | 10 | 26.3 | 59 | 27.4 | 54 | 23.9 | 0.739 |
| \(\geq10\text{ g dl}^{-1}\) | 28 | 73.7 | 152 | 70.7 | 165 | 73.0 |             |
| NA        | - | - | 4 | 1.9 | 7 | 3.1 |             |
| Platelet count |             |             |             |             |             |             |             |
| \(<400\text{ per}\mu\text{l}\) | 32 | 84.2 | 212 | 98.6 | 52 | 23.0 | <0.001 |
| \(\geq400\text{ per}\mu\text{l}\) | 6 | 15.8 | 42 | 19.5 | 37 | 16.4 |             |
| NA        | - | - | 4 | 1.9 | 7 | 3.1 |             |
| Koehne’s Prognostic Groups |             |             |             |             |             |             |             |
| Low       | 31 | 81.6 | 212 | 98.6 | 52 | 23.0 | <0.001 |
| Intermediate | 6 | 15.8 | 1 | 0.5 | 125 | 55.3 |             |
| High      | - | - | 2 | 0.9 | 31 | 13.7 |             |
| NA        | 1 | 2.6 | - | - | 18 | 8.0 |             |
| Treatment |             |             |             |             |             |             |             |
| FUFIIRI   | 23 | 60.5 | 94 | 43.7 | 121 | 53.5 | 0.045 |
| mIROX     | 15 | 39.5 | 121 | 56.3 | 105 | 46.5 |             |

Abbreviations: CEA — carcinoembryonic antigen; LDH — lactate dehydrogenase; FUFIIRI — 5-fluorouracil/folinic acid/irinotecan; mIROX — modified irinotecan plus oxaliplatin; NA — not assessable; WBC — white blood cell count. Statistically significant \(P\)-values are shown as bold entries.
Table 2. Best response (RECIST 1.1) according to subgroups

| Hepatic resection, n = 38 | LLD, n = 215 | Non-LLD, n = 226 |
|--------------------------|-------------|-----------------|
| n = 38 | n = 215 | n = 226 |
| % | % | % | P-value | P-value |
| CR 5 | 15.2 | 18 | 8.4 | 14 | 6.2 | 0.211 | 0.486 |
| PR 23 | 60.5 | 70 | 32.6 | 65 | 28.8 | 0.002 | 0.446 |
| SD 10 | 26.3 | 68 | 31.6 | 82 | 36.3 | 0.643 | 0.352 |
| PD — | — | 32 | 14.9 | 24 | 10.6 | 0.011 | 0.422 |
| NA — | — | 27 | 12.6 | 41 | 18.1 | 0.031 | 0.136 |

Abbreviations: CR = complete response; LLD = liver-limited disease; NA = not assessable; non-LLD = non-liver-limited disease; PD = progressive disease; PR = partial response; SD = stable disease. Response evaluation according to RECIST 1.1. Statistically significant P-values are shown as bold entries.

Table 3. Survival times according to subgroups

| Hepatic resection, n = 38 | LLD, n = 215 | Non-LLD, n = 226 | P-value |
|--------------------------|-------------|-----------------|--------|
| Median | 95% CI* | Median | 95% CI* | Median | 95% CI* | Log-rank |
| PFS 16.6 | 8.6–24.6 | 6.5 | 5.8–7.2 | 8.2 | 7.2–9.2 | <0.001 |
| OS 48.0 | 42.0–54.0 | 17.0 | 13.9–20.1 | 19.0 | 17.0–21.0 | <0.001 |

Abbreviations: CI = confidence interval; LLD = liver-limited disease; non-LLD = non-liver-limited disease; OS = overall survival; PFS = progression-free survival. *The P-value given in the last row of the table reflects the global log-rank P-value over the three subgroups.

Progression-free survival and overall survival according to Koehne’s risk groups. By applying risk classification according to Koehne et al, median PFS was 7.2 months in the low-risk group and 8.2 months in the intermediate-risk group. In high-risk patients, PFS was only 4.3 months (P = 0.015). Accordingly, OS was comparable between low- and intermediate-risk patients (21.5 months and 20.4 months), whereas high-risk patients had a significantly shortened OS of only 11.6 months (P < 0.001). (Table 5; Figure 2A; Figure for PFS not shown).

Prognostic factors for OS in LLD. By definition, the number of metastatic sites in LLD patients is ‘one’. As this parameter did not work as a differentiating prognostic factor, the Koehne model was not able to distinguish prognostic groups among the subgroup of LLD patients. This is demonstrated by the fact, that 99% of LLD patients showed low-risk characteristics according to this model (Table 1). Therefore a COX regression analysis was performed to obtain independent prognostic factors for LLD, patients including all available baseline characteristics shown in Table 1. Within the subgroup of LLD patients, elevated WBC count (HR 1.13; P = 0.005) and elevated LDH (HR 1.27; P = 0.018) were the only factors significantly associated with decreased overall survival. (Table 6).

Overall survival according to WBC count and LDH levels in LLD. According to the two prognostic factors found in the Cox regression analysis, LLD patients were subdivided into three groups: normal LDH level and WBC count (low risk), one abnormal parameter (intermediate risk) or both, WBC count and LDH levels elevated (high risk); low-risk patients had a
significantly prolonged median OS of 23.2 months compared with intermediate-risk patients (median OS 16.7 months). For high-risk patients, median OS was only 10.1 months. Multivariate HR was 1.69. (Table 7; Figure 2B).

Overall survival according to WBC count and LDH levels within the trial population. To evaluate WBC count and LDH levels also within the whole FIRE-1 study population, again three groups were built according to LDH and WBC baseline levels. For low-risk patients, median OS was 25.2 months. Intermediate-risk patients had median OS of 17.4 months, whereas high-risk patients had an inferior median OS of only 10.6 months. Multivariate HR was 1.68. (Table 7; Figure 2C).

**DISCUSSION**

Within the last 10 years, an increasing number of hepatic resections for colorectal liver metastases could be achieved by multidisciplinary teams including hepatobiliary surgeons and

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**Table 5. Survival times according to Köhne’s risk groups**

|          | Low risk, *n* = 295 | Intermediate risk, *n* = 132 | High risk, *n* = 33 | *P*-value |
|----------|---------------------|-----------------------------|---------------------|-----------|
| **PFS**  | Median 7.2          | 6.4–8.1                     | 6.2                 | 4.3       | 1.1–7.5 | 0.015 |
| **OS**   | 21.5                | 18.5–24.6                   | 20.4                | 18.4–22.3 | 11.6 | 8.4–14.8 | <0.001 |

Abbreviations: PFS = progression-free survival; OS = overall survival; CI = confidence interval.

*P*-value given in the last row of the table reflects the global log-rank *P*-value over the three subgroups.

**Table 6. Multivariate analysis: prognostic factors for survival (LLD only) (COX regression)**

|          | HR     | 95% CI       | *P*-value |
|----------|--------|--------------|-----------|
| WBC      | 1.13   | 1.04–1.23    | 0.005     |
| LDH      | 1.27   | 1.04–1.54    | 0.018     |

Abbreviations: CI = confidence interval; HR = Hazard ratio; LDH = lactate dehydrogenase; WBC = white blood cell count.

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Figure 2. (A) Overall survival in patients according to Köhne’s risk classification (FIRE-1 trial population; *n* = 479). (B) Overall survival according to FIRE prognostic score (LDH + WBC) (LLD population). (C) Overall survival according to FIRE prognostic score (LDH + WBC) (FIRE-1 trial population). Abbreviations: Low risk = WBC count and LDH levels not elevated; Intermediate risk = WBC count or LDH levels elevated; High risk = WBC count and LDH levels elevated; OS = overall survival.
medical oncologists improving survival in selected patients. Relating to this, it was shown that improved outcome of mCRC patients was associated with an increase in hepatic resection in two large cancer centers between 1998 and 2004 (Kopetz et al, 2009). In the present pre-planned subgroup analysis, we report from a randomised phase III trial that enrolled 479 patients from July 2000 to October 2004 (Fischer von Weikersthal et al, 2010). A total of 38 secondary hepatic resections could be performed resulting in a total resection rate of 7.9%. Within the range of published data, these patients showed favourable long-term survival with median OS of 48.0 months and a 5- and 10-year-survival rate of 39% and 17%, respectively (Rees et al, 2008; Vignano et al, 2012). After an extended follow-up time of almost 5 years and an event rate of 87.1%, the present study is based on very mature data. It is also important to note that primary resectability of metastatic disease was an exclusion criterion in the FIRE-1 trial.

Best response evaluation according to RECIST 1.1 confirms the concept of conversion chemotherapy also in the era before monoclonal antibodies could be combined with cytotoxic chemotherapy. Secondary resection of colorectal liver metastases could be achieved with complete response in 15.2%, partial response in 60.5% and stable disease in 26.3% of patients who then underwent hepatic resection. In light of these data, it is important to note that the patient with 'stable disease' should be evaluated for (technically) secondary resection by a multidisciplinary team. In the present study, we were able to identify five potential prognostic factors for secondary hepatic resection within our trial population: LLD, LDH, node-negative primary tumour, KPS and Age. Although LDH, KPS and AP constitute widely explored prognostic factors for OS, the finding of a node-negative primary tumour being associated with secondary hepatic resection confirms previous findings in resected patients where lymphatic spread of the primary was shown to be a risk factor (Nordlinger et al, 1996; Fong et al, 1999). Relating to this, also more than 75% of patients with secondary hepatic resection developed their (liver) metastases synchronously, which has been shown to display a genetically more aggressive tumour subtype but did not result in unfavourable OS according to a retrospective analysis of the CAIRO trial (Mekenkamp et al, 2010; Slesser et al, 2013). In our analysis of prognostic factors for secondary hepatic resection, LLD remains the strongest prognostic factor. This finding supports the ESMO guidelines requiring highly effective combination therapy to achieve resectability in potentially resectable group 1 patients (Schmolck et al, 2012).

Furthermore, the present study aimed to characterise the subgroup of patients with LLD mCRC. Although LLD patients from the CRYSTAL and OPUS trials have been previously indicated as a subgroup with superior benefit from chemotherapy (with or without cetuximab), the outcome in unresectable LLD remains unclear (Van Cutsem et al, 2011). The present analysis is, to the best of our knowledge, the first to describe a comparable outcome in non-resected LLD- and non-LLD patients in an irinotecan-based phase III trial. This finding emphasises the fact that LLD conversion into secondary resection by combination chemotherapy is the major goal. Based on the present data, we suggest the liver as the major life-limiting metastatic site in unresected or unresectable mCRC patients.

With the inapplicability of the KPS in LLD patients, our analysis also emphasises the need of customised prognostic scoring tools within this important subgroup. Although two previous analyses form French working groups were able to confirm WHO performance status as an independent prognostic factor, WBC count could not be evaluated by the GERCOR group because of missing data and LDH vice versa in the study performed by Desot et al (Chibaudel et al, 2011; Desot et al, 2013). In contrast, KPS was not found to be a prognostic factor in our analysis of 215 LLD patients, with the limitation that patients with KPS <60% were not included in the trial and the comparison between KPS, ECOG and WHO-PS constitute a difficult issue (Sorbye et al, 2007). In addition, it also needs to be taken into account that the differentiation between ECOG 1 and ECOG 2 is based on the subjective decision of the treating physician and often remains debatable in both, daily routine and clinical trials. With LDH levels and WBC count being used as a cut-off variable (WBC ≥8.000 per μl and LDH ≤250 U1⁻¹) measured at baseline, the use of these two objective laboratory prognostic factors seems to be advantageous (Sorbye et al, 2007).

Elevated LDH levels have been shown to be widely associated with poor outcome in several cancer entities including mCRC (Tas et al, 2001; Gerlinger et al, 2010; Chibaudel et al, 2011; Eigentler et al, 2011). Relating to this, elevated LDH levels in mCRC were linked to activation of hypoxia-inducible factor-related genes in aggressive tumour phenotypes bearing accelerated growth kinetics (Koukourakis et al, 2005). Notwithstanding, it is important to note that LDH may be also influenced by comorbidities such as systemic infection, bone marrow disorders and liver and lung insufficiency particularly outside of clinical trials, where exclusion criteria do not apply.

Also high levels of WBCs, absolute neutrophil count and neutrophil lymphocyte ratio are allied to poor survival in mCRC (Kohne et al, 2002; Sanoff et al, 2008; Proctor et al, 2012). Although the role of the innate immune system in cancer development, metastasis and tumour progression is incompletely understood, leucocytes have been found to be involved in progression phases of carcinogenesis by activation and stimulation of growth factors and angiogenesis (Balkwill, 2004; Shankar et al, 2006).

One limitation of the present analysis is the small fraction of patients who underwent hepatic surgery. Also, the decision to perform hepatic resection was not validated centrally, but was taken in the local trial centres by oncologists and hepatobiliary surgeons. Therefore, an independent review of hepatic imaging and response as well as independent surgical review on respectability could not be performed in our patients. It is also important to note that in this trial mainly patients with good performance status

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**Table 7. Overall survival according to WBC and LDH (FIRE score)**

| Overall survival | Low risk | Intermediate risk | High risk | P-value |
|-----------------|----------|------------------|-----------|---------|
| LLD patients (n = 215) | Median 23.2 | 95% CI* 18.1–28.1 | Median 16.7 | 95% CI* 13.2–20.1 | Median 10.1 | 95% CI* 5.9–14.4 | <0.001 |
| FIRE-1 trial (n = 479) | Median 25.2 | 95% CI* 22.9–27.6 | Median 17.4 | 95% CI* 15.3–19.4 | Median 10.6 | 95% CI* 7.8–13.8 | <0.001 |

**Abbreviations:** CI = confidence interval; High risk = WBC and LDH elevated; Intermediate risk = WBC or LDH elevated; LLD = liver-limited disease; Low risk = WBC and LDH not elevated; OS = overall survival. *The P-value given in the last row of the table reflects the global log-rank P-value over the three subgroups.
(KPS 100% in 63% of patients) underwent hepatic resection. This also may have influenced the OS in this subgroup as well as the OS in the whole trial population. But as surgical intervention may outline a selection process per se, this may concern many survival reports on patients with metastasectomy. Second, the findings of prognostic factors in LLD patients are only suggestive and need to be confirmed and validated in further analyses. In this regard, further research on conversion chemotherapy is needed to define the optimal regimen leading to secondary resectability and long-term survival.

The proposed prognostic score is based on two baseline parameters, LDH and WBC count, which can easily be obtained and reproduced. Application of this score may help to select patients within clinical trials and may contribute to an optimisation of conversion therapy for mCRC patients.

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CONFLICT OF INTEREST

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