Randomized phase III trial in elderly patients comparing LV5FU2 with or without irinotecan for first-line treatment of metastatic colorectal cancer (FFCD 2001–02)


1Department of Gastroenterology, CHU Avicenne, APHP and University Paris 13, Sorbonne Paris Cité, Bobigny; 2Department of Oncology, CHU Dupuytren, Limoges; 3Department of Gastroenterology, CHU Saint Etienne–Hôpital Nord, Saint Priest en Jarez; 4FFCD Data Center, Fédération Francophone de Cancérologie Digestive, Dijon; 5Department of Gastroenterology, CHU Le Bocage, Dijon; 6Department of Gastroenterology, CH Blois, Blois; 7Department of Gastroenterology, CHU Hôpital Nord, Marseille; 8Department of Gastroenterology, CH Meaux, Meaux; 9Department of Gastroenterology, CHU Haut Lévêque, Pessac; 10Department of Gastroenterology, CHU Charles Nicolle, Rouen; 11Department of Gastroenterology, CH Saint Jean, Perpignan; 12Department of Gastroenterology, CHU Trousseau, Tours; 13Department of Oncology, CH Chambery, Chambery; 14Department of Gastroenterology, CH Pasteur, Colmar; 15Department of Gastroenterology, CHU Haut Lévêque, Pessac; 16Department of Digestive Oncology, CHU Georges Pompidou, APHP, Paris; 17Department of Gastroenterology, CH Duchenne, Boulogne sur Mer; 18Department of Oncology, Clinique Bonnefond, Alès; 19Department of Gastroenterology, CHU Nancy, Vandoeuvre-les-Nancy; 20Department of Gastroenterology, CH Avignon, Avignon; 21Department of Gastroenterology, CHU Robert Debré, Reims; 22Department of Gastroenterology, CHU Henri Mondor, APHP, Créteil; 23Department of Oncology, Institut Curie, Saint-Cloud; 24University Versailles–St Quentin, St Quentin, France

Background: Metastatic colorectal cancer (mCRC) frequently occurs in elderly patients. However, data from a geriatric tailored randomized trial about tolerance to and the efficacy of doublet chemotherapy (CT) with irinotecan in the elderly are lacking. The benefit of first-line CT intensification remains an issue in elderly patients.
Patients and methods: Elderly patients (75+) with previously untreated mCRC were randomly assigned in a 2 × 2 factorial design (four arms) to receive 5-FU (5-fluorouracil)-based CT, either alone (FU: LV5FU2 or simplified LV5FU2) or in combination with irinotecan [IRI: LV5FU2–irinotecan or simplified LV5FU2–irinotecan (FOLFIRI)]. The CLASSIC arm was defined as LV5FU2 or LV5FU2–irinotecan and the SIMPLIFIED arm as simplified LV5FU2 or FOLFIRI. The primary end point was progression-free survival (PFS). Secondary end points were overall survival (OS), safety and objective response rate (ORR).

Results: From June 2003 to May 2010, 71 patients were randomly assigned to LV5FU2, 71 to simplified LV5FU2, 70 to LV5FU2–irinotecan and 70 to FOLFIRI. The median age was 80 years (range 75–92 years). No significant difference was observed for the median PFS: FU 5.2 months versus IRI 7.3 months, hazard ratio (HR) = 0.84 (0.66–1.07), P = 0.15 and CLASSIC 6.5 months versus SIMPLIFIED 6.0 months, HR = 0.85 (0.67–1.09), P = 0.19. The ORR was superior in IRI (P = 0.0003): FU 21.1% versus IRI 41.7% and in CLASSIC (P = 0.04): CLASSIC 37.1% versus SIMPLIFIED 25.6%. Median OS was 14.2 months in FU versus 13.3 months in IRI, HR = 0.96 (0.75–1.23) and in 15.2 months in CLASSIC versus 11.4 months in SIMPLIFIED, HR = 0.71 (0.55–0.92). More patients presented grade 3–4 toxicities in IRI (52.2% versus 76.3%).

Conclusion: In this elderly population, adding irinotecan to an infusional 5-FU-based CT did not significantly increase either PFS or OS. Classic LV5FU2 was associated with an improved OS compared with simplified LV5FU2.

Clinicaltrials.gov: NCT00303771.

Key words: elderly, colorectal cancer, chemotherapy, geriatric oncology

introduction

Colorectal cancer occurs mainly in elderly patients. Recent estimations showed that, in France, 45% of patients diagnosed with colorectal cancer are 75 years old or older (http://www.invs.sante.fr/applications/cancers/projections2010). Specific data for the treatment of metastatic colorectal cancer (mCRC) in elderly patients are scarce. Until recently, elderly patients were underrepresented in clinical trials [1]. Moreover, the main studies that established the intensification of chemotherapy included few or highly selected elderly patients [2, 3]. In a series of selected fit elderly patients, irinotecan or oxaliplatin combined with fluorouracil chemotherapy was well tolerated and was as effective as in younger patients [4]. A post hoc analysis of randomized clinical trials comparing combined irinotecan and fluorouracil versus fluorouracil alone suggested that the benefit of irinotecan on progression-free survival (PFS) and overall survival (OS) was preserved in patients over 70 years [5]. Nevertheless, patients over 75 years represented only 6.9% of the randomized patients. A prospective phase II study evaluated the FOLFIRI regimen in patients over 70 years and concluded that the treatment was well tolerated and effective in selected elderly patients [6]. A post hoc analysis of randomized trials comparing doublet with oxaliplatin versus fluorouracil alone suggest that the benefit of oxaliplatin is preserved in patients over 70 years [7]. Nevertheless, a randomized phase III study specific for frail or elderly patients did not demonstrate a significant gain in PFS or OS of fluoropyrimidine + oxaliplatin compared with fluoropyrimidine alone for mCRC treatment [8]. The benefit of doublet chemotherapy is therefore a concern in elderly patients. Moreover, doublet chemotherapy with irinotecan had never been compared in a prospective randomized trial in elderly patients. Age threshold for specific care in elderly patients is a matter of debate. The threshold for geriatric oncology trials is usually 70 or 75 [9]. A threshold of 75 years was chosen by the French authorities to define oncogeriatrics, as frailty and comorbidities are more frequent than in patients aged 70–75.

Bolus fluorouracil is associated with increased toxicity in elderly patients [10]. The bimonthly fluorouracil and leucovorin regimen ‘LV5FU2’, which associates 2 days of bolus fluorouracil and 2 days of fluorouracil over 22 h of continuous infusion, is less toxic than the monthly 5-day bolus fluorouracil regimen [11]. The LV5FU2 regimen was modified in that the D2 fluorouracil bolus was suppressed and the continuous infusion of fluorouracil increased to 46 h in order to be less burdensome for the patients. This ‘simplified LV5FU2’ regimen was combined with irinotecan to become FOLFIRI [12]. Nevertheless, the simplified LV5FU2 regimen has never been directly compared with the classic LV5FU2 with or without irinotecan.

The FFCD 2001–02 trial is a randomized phase III study evaluating chemotherapy with classic LV5FU2 regimen or simplified LV5FU2 regimen with or without irinotecan in patients with mCRC aged 75 or more. A preliminary analysis of the geriatric factors revealed that cognitive and functional impairment were predictive of severe toxicity or unexpected hospitalization [13]. The main analysis is presented here.

patients and methods

patient selection

Patients aged ≥75 years with histologically confirmed unresectable mCRC were eligible (supplementary Material, available at Annals of Oncology online), and written informed consent was obtained for each patient. The study was approved by the Ethics Committee (CPPRB Boulogne Billancourt no 020946 in 26 September 2002).

study design

This phase III trial was a 2 × 2 factorial design (four arms) combining 5-FU-based CT, either alone (FU arms: LV5FU2 or simplified LV5FU2) or in combination with irinotecan (IRI arms: LV5FU2–irinotecan or FOLFIRI). The second comparison was CLASSIC arms (LV5FU2 or LV5FU2–irinotecan) versus SIMPLIFIED arms (simplified LV5FU2 or FOLFIRI). Patients were randomly assigned to one group, randomization was stratified according to center, Charlson index (0 versus 1–2 versus 3+), Karnofsky index (60–70 versus 80–90 versus 100), previous adjuvant CT, sex, age (<80 versus ≥80 years) and alkaline phosphatases (≤2 × upper limit of normal (LN) versus >2 × LN).

original articles

Annals of Oncology
treatment plan and evaluation

Treatments are detailed in supplementary Material, available at Annals of Oncology online. All toxicities were graded according to the US National Cancer Institute Common Toxicity Criteria (version 2.0). Serious adverse events were also reported. Radiological assessments were carried out every 8 weeks (abdominal and thoracic computed tomography scan or magnetic resonance imaging) and tumor response was classified according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria (version 1.0).

statistical analysis

This trial was designed to compare PFS between two arms: FU and IRI or CLASSIC and SIMPLIFIED. To demonstrate an improvement in the median PFS from 5.5 to 7.9 months; 240 events for two arms (282 patients for two arms) were required (two-sided α = 5%, β = 80%).

The primary end point, PFS, was defined as the time from randomization to first progression (defined by RECIST 1.0 criteria) or death (all causes). Patients alive without progression were censored at the last follow-up date.

Secondary end points were OS, defined as the time between randomization and death (all causes), objective response rate (ORR) and tolerance. Statistics are detailed in supplementary Material, available at Annals of Oncology online.

A planned interim analysis, based on safety data only reviewed by an independent committee, was carried out after the inclusion of 142 patients and led to continuation of the trial [14]. The cut-off date for the final analysis was 5 May 2011.

classic results

baseline characteristics

Between June 2003 and May 2010, 71 patients were randomly assigned to LV5FU2, 71 to simplified LV5FU2, 70 to LV5FU2–irinotecan and 70 to FOLFIRI by 50 French centers (Figure 1). The four groups were well balanced with regard to baseline characteristics (supplementary Table S1, available at Annals of Oncology online). The median age was 80 years (range 75–92 years).

282 patients randomly assigned to treatment

<table>
<thead>
<tr>
<th>FU arms</th>
<th>IRI arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 142</td>
<td>N = 140</td>
</tr>
</tbody>
</table>

- LV5FU2 | Simplified LV5FU2 |
| N = 71  | N = 71           |
- 3 untreated: -1 refused to be treated -1 without cancer -1 unknown reason
- 2 untreated: -1 refused to be treated -1 without cancer -1 unknown reason

- LV5FU2–irinotecan
| N = 70 |
- 2 untreated: -1 refused to be treated -1 without cancer -1 unknown reason

- FOLFIRI
| N = 70 |
- 3 untreated: -2 lost to follow-up -1 unknown reason

Figure 1. Flow chart (CONSORT diagram).

treatment administration

Six patients in FU and five patients in IRI arm were not treated (Figure 1). The median duration of the treatment was 3.5 months (range 0–23.6 months) in FU, 4.5 months (range 0–23.0 months) in IRI, 4.5 months (range 0–23.0 months) in CLASSIC and 3.6 months (range 0–23.6 months) in SIMPLIFIED (supplementary Table S2, available at Annals of Oncology online). The planned irinotecan dose escalation from 150 to 180 mg/m² was performed in 56 (41.5%) patients with IRI. Treatment interruption was mainly due to disease progression in both arms. Nevertheless, there were more treatment interruptions for toxicity and patient refusal in IRI (supplementary Table S3, available at Annals of Oncology online).

efficacy results

progression-free survival. The test for interaction was not significant (P = 0.44). No statistical difference was found: hazard ratio (HR) 0.84 [95% confidence interval (CI) 0.66–1.07], P = 0.15. Median PFS in FU was 5.2 months (95% CI 3.9–6.1) versus 7.3 months (95% CI 6.5–8.6) in IRI (supplementary Figure S1, available at Annals of Oncology online, and Table 1). The 6-month PFS rate was in favor of IRI. The ‘per-protocol’ analysis in 258 patients (126 in FU and 132 in IRI) confirmed the ITT results with a median PFS of 5.31 months in FU versus 7.54 months in IRI: HR 0.79 (95% CI 0.62–1.01), P = 0.06. The CLASSIC versus SIMPLIFIED comparison revealed no statistical difference for PFS: HR 0.85 (95% CI 0.67–1.09), P = 0.19. Median PFS in CLASSIC was 6.5 months (95% CI 4.9–7.4) versus 6.0 months (95% CI 4.8–7.7) in SIMPLIFIED. The results for the four arms are presented in supplementary Table S4, available at Annals of Oncology online.

overall survival. The test for interaction was not significant (P = 0.50). Overall median follow-up was 69.8 months (95% CI 43.4–83.9). Median OS did not differ significantly between FU
and IRI: HR 0.96 (95% CI 0.75–1.24), P = 0.77 (supplementary Figure S1, available at Annals of Oncology online, and Table 1). The per-protocol analysis gave the same results with no difference in OS: 14.72 months (95% CI 9.76–19.45) in FU versus 14.95 months (95% CI 12.29–18.46) in IRI. The comparison between CLASSIC versus SIMPLIFIED revealed a significantly longer OS in CLASSIC: HR 0.71 (95% CI 0.55–0.92), P = 0.01. Median OS in CLASSIC was 15.2 months (95% CI 12.6–19.7) versus 11.4 months (95% CI 9.2–15.7) in SIMPLIFIED. The results for the four arms are presented in supplementary Table S4, available at Annals of Oncology online.

response rate. The test for interaction was not significant (P = 0.80). Irinotecan significantly improved ORR. The observed ORR was 21.1% (95% CI 14.5–29.0) in FU versus 41.7% (95% CI 33.2–50.6) in IRI (P = 0.0003) (Table 1). Surgical resection of the metastases was performed in 3 (2.1%) patients in FU and in 4 (2.9%) in IRI. A higher response rate was observed in CLASSIC versus SIMPLIFIED (37.1% versus 25.6%; P = 0.04).

tolerance
Toxicities were evaluated for all the patients who received at least one dose of chemotherapy. More patients in IRI presented grade 3–4 toxicities (76.3% versus 52.2%) (supplementary Table S5, available at Annals of Oncology online). Median time to the onset of grade 3–4 all toxicities was 218 days in FU versus 59 days in IRI (P < 0.0001) (supplementary Figure S2A, available at Annals of Oncology online). Toxic death occurred in two patients in each group. There was no difference between CLASSIC and SIMPLIFIED for toxicity

<table>
<thead>
<tr>
<th>Table 1. Efficacy results for PFS, OS and ORR</th>
<th>FU (N = 142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival</td>
<td>IRI (N = 140)</td>
</tr>
<tr>
<td>N. of events (death or progression)</td>
<td>137</td>
</tr>
<tr>
<td>Median in months (95% CI)</td>
<td>5.2 (3.9–6.1)</td>
</tr>
<tr>
<td>6-month survival (95% CI)</td>
<td>42.5% (34.2–50.5)</td>
</tr>
<tr>
<td>12-month survival (95% CI)</td>
<td>17.3% (11.5–24.0)</td>
</tr>
</tbody>
</table>

| Overall survival                              |             |         |
| N. of events (death)                          | 129         | 121     | 0.77   |
| Median in months (95% CI)                    | 14.2 (9.5–19.0)| 13.3 (11.2–17.9)| 0.77 |
| 12-month survival (95% CI)                    | 53.3% (44.6–61.1)| 57.1% (48.5–64.9)| 0.77 |
| 24-month survival (95% CI)                    | 29.3% (21.8–37.2)| 22.9% (16.0–30.5)| 0.77 |

| Tumor response, N (%)                        |             |         |
| Objective response (CR and PR)               | 28 (21.1)   | 55 (41.7)| 0.0003 |
| CR                                            | 3 (2.3)     | 6 (4.6)  |          |
| PR                                            | 25 (18.8)   | 49 (37.1)|          |
| SD                                            | 59 (44.4)   | 43 (32.6)|          |
| PD                                            | 34 (25.6)   | 16 (12.1)|          |
| NE                                            | 12 (9.0)    | 18 (13.6)|          |

| Comparison CLASSIC versus SIMPLIFIED         |             |         |
| Progression-free survival                    |             |         |
| N. of events (death or progression)          | 136         | 134     | 0.19   |
| Median in months (95% CI)                    | 6.5 (4.9–7.4)| 6.0 (4.8–7.7)| 0.19 |
| 6-month survival (95% CI)                    | 54.3% (45.7–62.1)| 49.7% (41.1–57.6)| 0.19 |
| 12-month survival (95% CI)                   | 22.9% (16.3–30.1)| 13.7% (8.6–19.9)| 0.19 |

| Overall survival                              |             |         |
| N. of events (death)                          | 122         | 128     | 0.01   |
| Median in months (95% CI)                    | 15.2 (12.6–19.7)| 11.4 (9.2–15.7)| 0.01 |
| 12-month survival (95% CI)                    | 62.9 (54.3–70.3)| 47.5 (39.0–55.5)| 0.01 |
| 24-month survival (95% CI)                    | 31.3 (23.6–39.4)| 20.9 (14.4–28.3)| 0.01 |

| Tumor response, N (%)                        |             |         |
| Objective response (CR and PR)               | 49 (37.1)   | 34 (25.6)| 0.04   |
| CR                                            | 7 (5.3)     | 2 (1.5)  |          |
| PR                                            | 42 (31.8)   | 32 (24.1)|          |
| SD                                            | 48 (36.4)   | 54 (40.6)|          |
| PD                                            | 23 (17.4)   | 27 (20.3)|          |
| NE                                            | 12 (9.1)    | 18 (13.5)|          |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; FU, fluorouracil; IRI, irinotecan; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; CI, confidence interval.
second and further lines of chemotherapy

The ORR observed following second-line chemotherapy was 13.2% in FU, 13.5% in IRI and 13.0% in CLASSIC and 13.8% in SIMPLIFIED (supplementary Table S6, available at Annals of Oncology online). During the whole lifetime, 17 (12%) patients in FU, 43 (31%) in IRI, 35 (25%) in CLASSIC and 25 (18%) patients in SIMPLIFIED were exposed sequentially to both irinotecan and oxaliplatin.

analysis of prognostic factors

univariate analysis. Less than two metastatic sites, alkaline phosphatases ≤ 2 LN, leukocytes ≤ 11 × 109/l, carcinoembryonic antigen (CEA) ≤ 2 LN and carbohydrate antigen 19.9 ≤ 2 LN were associated with both prolonged PFS and OS. Moreover, CLASSIC group and 100% Karnofsky index were associated with prolonged OS (supplementary Table S7, available at Annals of Oncology online).

multivariate analysis. To explore potential prognostic factors of PFS and OS, a model was constructed with baseline clinical parameters significant in univariate analysis and with treatment arm. When IRI was compared with FU, the multivariate Cox analysis showed that alkaline phosphatase ≤ 2 LN and CEA ≤ 2 LN were associated with prolonged PFS. Alkaline phosphatase ≤ 2 LN, CEA ≤ 2 LN and < 2 metastatic sites were associated with prolonged OS (supplementary Table S7, available at Annals of Oncology online).

When CLASSIC was compared with SIMPLIFIED, alkaline phosphatase ≤ 2 LN and CEA ≤ 2 LN were associated with prolonged PFS. CLASSIC group, alkaline phosphatase ≤ 2 LN, CEA ≤ 2 LN and < 2 metastatic sites were associated with prolonged OS.

subgroup analysis. There was no significant difference in treatment effect for either PFS (supplementary Figure S3A and C, available at Annals of Oncology online) or OS (supplementary Figure S3B and D, available at Annals of Oncology online) according to the considered covariates (supplementary Table S8, available at Annals of Oncology online).

discussion

This is the first randomized prospective study specifically conducted in mCRC patients aged 75 or over. The main result of the study was that adding irinotecan to fluorouracil in the first line did not significantly prolong PFS. Our results are in line with the only other prospective study that compared fluoropyrimidine monotherapy with doublet chemotherapy (oxaliplatin-based) in 470 patients who were frail or aged over 70 [8]. In both studies, a trend toward an improvement in PFS was observed. A post hoc analysis of prospective trials with no specific age groups, which compared a combination of irinotecan plus fluorouracil with fluorouracil alone, showed that irinotecan improved PFS in patients over 70 years but not in patients over 75 years. The lack of difference in the older patients may have been due to their small number [5]. The PFS in both arms of this pooled analysis was longer than in both arms in our study. This could be explained by the highly selected patients in the former study. Our study may be more representative of real life for elderly patients. This underlines the need to conduct specific studies in elderly patients. The HR for PFS in all these studies are very close and always in favor of doublet chemotherapy: 0.84 in the FOCUS 2 study [8], 0.80 in the pooled analysis of irinotecan studies [5] and 0.84 in our study. It must be pointed out that the improvement in the time to disease progression in the irinotecan registration study in 387 patients was 2.3 months [3], which is very close to our result of 2.1 months. Our hypothesis was to improve PFS by 2.4 months, but this resulted in a sample size that was possibly too small. Thus, our study, like the FOCUS 2 study, might have been underpowered compared with the registration trials. Moreover, a recent compilation of published data of all of the above trials in elderly patients, including our study, suggested that doublet chemotherapy prolonged PFS: HR = 0.82 (95% CI 0.72–0.93) [15].

In our study, as in the FOCUS 2 study [8], there was clearly no effect of first-line doublet chemotherapy on OS. These two studies were not powered to demonstrate an OS benefit. Nevertheless, no OS advantage was observed in the compilation of published data, which included 1225 patients [15]. It must be pointed out that, in the FFCD 2001–02 study, 52% of the patients in the 5-FU arm received second-line chemotherapy. This high proportion of second-line therapy even in this elderly population could explain the lack of a survival advantage with first-line doublet chemotherapy. Several studies have demonstrated that OS in patients receiving a sequential treatment starting with fluoropyrimidine monotherapy was not improved by first-line doublet chemotherapy [16–18]. In our study, OS in combination arm was in line with previous phase II studies that evaluated fluoropyrimidine plus irinotecan in elderly patients [19, 20]. Nevertheless, OS was shorter than the 17.4 months OS observed in the Douillard et al.’s study [3]. This observation suggests that age remains a prognostic factor even in the metastatic setting. Several hypotheses, such as comorbidity-related impairment, a high rate of dose reduction or cancer-unrelated death, could be made to explain this poor result. Unfortunately, cancer-unrelated death was not collected in our study. Moreover, OS was slightly shorter than the 14.5 OS observed in the Folprecht et al.’s analysis [5]. This suggests that the results of non-geriatric specific studies are not reproducible in general geriatric populations.

In our study, the response rate achieved with fluorouracil plus irinotecan was higher than with fluorouracil alone. This result shows that the benefit of doublet chemotherapy for tumor shrinkage is sustained even in elderly patients. The same observation was reported in the FOCUS 2 trial [8]. Nevertheless, this higher response rate did not lead to a significant difference in surgical cure of metastases.

In our study, an OS benefit was observed in patients treated with CLASSIC. Surprisingly, there was no PFS advantage with CLASSIC despite a higher response rate. PFS is claimed to be a surrogate for OS [21]. Nevertheless, a recent large randomized trial reported prolonged OS in an experimental arm with no PFS or ORR improvement [22]. There is no obvious explanation for the prolonged OS with CLASSIC. It has been hypothesized that the depth of response may explain an OS advantage with no
PFS benefit. Unfortunately, depth of response was not assessed in our study. It must be pointed out that there were some slight differences between CLASSIC and SIMPLIFIED. There was a trend for more patients over 80 years, more females, a greater number of metastatic sites, less second- and third-line therapy in SIMPLIFIED.

More toxicities were observed in IRI and the time to toxicity occurrence was shorter in IRI. Febrile neutropenia was observed in 7.4% of patients in IRI group, which is higher than the 5.5% observed in the Douillard et al.’s study [3]. Thus, caution should be exercised before administering combination therapy in elderly and prophylactic treatment with granulocyte-colony stimulating factor should be considered. It must be pointed out that some geriatric parameters could predict the occurrence of toxicity independently of the treatment arm [13]. Toxicities were not reduced in SIMPLIFIED as it was expected.

Our study did not involve targeted therapy. Up to the end of our inclusion period, targeted therapy was seldom used in elderly patients. A survey of all French incident cases of mCRC in 2009 revealed that only 20% of elderly patient treated for mCRC received bevacizumab associated with first-line chemotherapy [23]. A recent phase III study reported a PFS improvement with the adjunction of bevacizumab to capecitabine therapy [23]. A recent phase III study reported a PFS improvement with the adjunction of bevacizumab to capecitabine therapy [23]. A recent phase III study reported a PFS improvement with the adjunction of bevacizumab to capecitabine therapy [23]. A recent phase III study reported a PFS improvement with the adjunction of bevacizumab to capecitabine therapy [23]. A recent phase III study reported a PFS improvement with the adjunction of bevacizumab to capecitabine therapy [23].

In conclusion, our study demonstrated that irinotecan combined with fluorouracil as the first-line chemotherapy for mCRC did not improve PFS or OS in elderly patients aged 75 years or more but increased toxicity. The superiority of classic LV5FU2 regimen for OS should be confirmed by another study and should be balanced by convenience and lower cost of the simplified regimen.

**References**


**Acknowledgements**


**Funding**

Supported by grant no. WPO/N-1720371 from Pfizer.

**Disclosure**

TA has received grants from Roche and Amgen and honoraria for presentations or advisory boards from Roche, Sanofi, Novartis and Merck Sereno. CL has received honoraria for presentations or advisory boards from Roche, Merck Sereno, Sanofi and Novartis. JP has received honoraria for a presentation for Amgen. J-LL has received honoraria from Sanofi, Lilly and Novartis. OB has received honoraria from Roche, Merck Sereno and Bayer. EMM has received honoraria from Sanofi.
Comprehensive analyses using next-generation sequencing and immunohistochemistry enable precise treatment in advanced gastric cancer

Y. Kuboki1,2,3,4, S. Yamashita5, T. Niwa5, T. Ushijima5, A. Nagatsuma2, T. Kuwata2, T. Yoshino4, T. Doi1,4, A. Ochiai2,3 & A. Ohtsu6*

1Department of Experimental Therapeutics, National Cancer Center Hospital East, Chiba; 2Division of Pathology, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba; 3Medical Science Program, Graduate School of Medicine, Keio University, Tokyo; 4Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba; 5Division of Epigenomics, National Cancer Center Research Institute, Tokyo; 6Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Chiba, Japan

Received 11 August 2015; revised 4 October 2015; accepted 9 October 2015

Background: In advanced gastric cancer (AGC), most clinical trials are designed on the basis of protein expression or gene amplification of specific genes. Recently, next-generation sequencing (NGS) allowed us to comprehensively profile the tumor gene status. This study aimed to elucidate the profiling between gene alterations and protein expression in AGC to aid in future clinical trials on AGC.

Patients and methods: Formalin-fixed, paraffin-embedded tumor samples from 121 stage III/IV gastric cancer patients were examined for protein expression of tyrosine kinase receptors (RTKs; ERBB2, EGFR, c-MET, and FGFR2) using immunohistochemistry (IHC). Furthermore, 409 cancer-related genes were sequenced to detect mutations and copy number variations using NGS.

Results: Most ERBB2 overexpression (IHC 3+) cases (80.0%) had ERBB2 amplification and did not have other RTK amplification or oncogene mutations. However, one-fourth of MET overexpression cases (25.0%) had ERBB2 alterations. EGFR and FGFR2 overexpression cases had ERBB2 alterations or other gene alterations such as KRAS or PIK3CA. On the other hand, most of the four RTK amplification cases (88.2%) were mutually exclusive with each amplification.


