**SUPPLEMENTARY MATERIALS**

**Overall survival prediction and usefulness of second-line chemotherapy in advanced pancreatic adenocarcinoma**

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**Supplementary Methods**

# **Procedures**

In the development cohort, patients were identified through the computer software of chemotherapy prescription used at Besancon Hospital (Bonnes Pratiques de la Chimiothérapie - BPC®, SQLI). In this software, patients were prospectively registered when their chemotherapy started. In the external validation cohort, patients were prospectively identified through the computer software of chemotherapy prescription used at Institute Mutualiste Montsouris, Henri Mondor University Hospital, and Reims University Hospital (CHIMIO®, Computer Engineering).

In both cohorts, patients were treated according to standard approved chemotherapy protocols, according to the recommendations of the National French thesaurus of digestive cancer (TNCD). A CT-scan assessment was performed every 3 months. A progression under first-line chemotherapy was defined radiologically with RECIST v1.1 criteria, and a progression under second-line chemotherapy could be determined radiologically or clinically. All therapeutic decisions were discussed and validated during digestive oncology-dedicated multidisciplinary meetings. Database was locked on December 31, 2015 for the development cohort and on June 30, 2016 for the external validation cohort.

The database was registered and declared to the National French Commission for bioinformatics data and patient liberty (CNIL).

# **Statistical analyses interpretation**

## *Discrimination*

The discrimination refers to the ability of separating patients with different prognosis. The C-index estimates the proportion of all pairwise patient combinations from the sample data whose survival time can be ordered according to whether the patient with the highest predicted survival is the one who actually survived longer (discrimination). The C-index (0 ≤ C ≤ 1) is a probability of concordance between predicted and observed survival, with C-index = 0.5 for random predictions and C-index = 1 for a perfectly discriminating model. In this study, the C-index calculation was repeated 1,000 times in random samples of the initial dataset with the use of bootstrap sampling procedures to derive 95% percentile confidence intervals for the C-index.

## *Calibration*

Calibration and goodness-of-fit refer to the ability to provide unbiased survival predictions in groups of similar patients. A prediction model is considered “well-calibrated” if the difference between predictions and observations in all groups of similar patients is close to 0 (perfect calibration).

## *Bootstrapping*

Bootstrapping is the preferred simulation technique that was first described by Bradley Efron (1). The original dataset is a random sample of patients being representative of a general population. Bootstrapping means generating a large number of datasets, each of which with the same sample size as the original one, by resampling with replacement (i.e., a previously selected patient may be selected again).

## *Internal validation*

Internal validation is useful to obtain an honest estimation of the model performance for patients that are similar to those in the development sample and to indicate an upper limit to the expected performance in other settings. The bootstrap approach is the preferred technique to assess internal validity.

## *External validation*

External validation may show different results from internal validation, since many aspects may be different between settings, including selection of patients, definition of variables, and diagnostic or therapeutic procedures. The strength of the evidence for the score validity is usually considered to be stronger with a fully external validation (other investigators, centers, etc.).

## *Continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI)*

The cNRI quantifies the direction of change, and the IDI the magnitude of change. When significantly greater than 0, IDI and cNRI suggest the existence of a net benefit from adding the marker of interest to the reference model.

# **Supplementary analyses for clinico-biological model**

The discrimination ability of this clinico-biological model was similar to the clinical model (C-index = 0.76; 95% bootstrap percentile confidence interval 0.72 to 0.80). As the final model without biological parameters, a sensitivity analysis was performed to validate the robustness of our final model with biological parameters, with a stratified but also with a frailty approach by using a random component for the hazard function based on the L2 regimen in the Cox model. Associations remained unchanged for the univariate and the multivariate analyses (**Supplementary Table 10**).

To assess potential bias arising from missing data for parameters involved in the multivariate final model on their significance (p-value) and their estimate (β and its standard error (SE)), a multiple imputation procedure with a Markov chain Monte Carlo (MCMC) method was performed using SAS MI and MIANALYZE procedure. This multiple imputation analysis based on 500 imputed datasets provides for all the variables similar results than the complete-subject analysis in term of significance for the association (p-value) and for coefficient estimations (β and SE) (**Supplementary Table 11**).

# **References**

1. Efron B (1979) Bootstrap Methods: Another Look at the Jackknife. Ann Stat 7: 1–26.

2. Collins GS, Ogundimu EO, Altman DG. Sample size considerations for the external validation of a multivariable prognostic model: a resampling study: Sample size considerations for validating a prognostic model. Stat Med. 2016 Jan 30;35(2):214–26.

**Supplementary Tables**

# **Supplementary Table 1. Patients characteristics according to the cohort set**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | | **Development set cohort**  **(N = 261)** | **External validation set cohort**  **(N = 163)** | **P\*** |
| Demographic parameters | |  |  |  |
| Age, median [IQR], years | | 65.8 [60.3 - 72.9] | 67.2 [60.9 - 74.0] | 0.29 |
| Sex, N (%) | |  |  | 0.23 |
|  | Male | 158 (60.5) | 89 (54.6) |  |
|  | Female | 103 (39.5) | 74 (45.4) |  |
| Smoking status, N (%) | |  |  | 0.11 |
|  | Never smoker or former smoker | 200 (76.9) | 135 (83.3) |  |
|  | Current smoker | 60 (23.1) | 27 (16.7) |  |
|  | Missing | 1 | 1 |  |
| Pathologic parameters at diagnosis of cancer | |  |  |  |
| Primary tumor site, N (%) | |  |  | 0.24 |
|  | Head | 152 (58.9) | 86 (53.1) |  |
|  | Body and/or Tail | 106 (41.1) | 76 (46.9) |  |
|  | Missing | 3 | 1 |  |
| Stages, N (%) | |  |  | 0.01 |
|  | Localized | 66 (25.3) | 23 (14.1) |  |
|  | Locally advanced | 61 (23.4) | 56 (34.4) |  |
|  | Metastatic | 134 (51.3) | 84 (51.5) |  |
| Tumor extension at the beginning of L2 | |  |  |  |
| Number of metastatic sites, N (%) | |  |  | 0.46 |
|  | 0 - 1 | 162 (62.1) | 107 (65.6) |  |
|  | ≥ 2 | 99 (37.9) | 56 (34.4) |  |
| Liver metastases, N (%) | |  |  | 0.07 |
|  | No | 106 (4.6) | 52 (31.9) |  |
|  | Yes | 155 (59.4) | 111 (68.1) |  |
| Peritoneal metastases, N (%) | |  |  | 0.82 |
|  | No | 162 (62.1) | 103 (63.2) |  |
|  | Yes | 99 (37.9) | 60 (36.8) |  |
| Lung metastases, N (%) | |  |  | 0.39 |
|  | No | 204 (78.2) | 133 (81.6) |  |
|  | Yes | 57 (21.8) | 30 (18.4) |  |
| Clinical parameters at the beginning of L2 | |  |  |  |
| Performance status (WHO), N (%) | |  |  | 0.09 |
|  | 0 | 47 (18.7) | 24 (14.7) |  |
|  | 1 | 118 (47.0) | 66 (40.5) |  |
|  | ≥ 2 | 86 (34.3) | 73 (44.8) |  |
|  | Missing | 10 | 0 |  |
| Pain†, N (%) | |  |  | 0.08 |
|  | No | 119 (47.6) | 92 (56.4) |  |
|  | Yes | 131 (52.4) | 71 (43.6) |  |
|  | Missing | 11 | 0 |  |
| Jaundice, N (%) | |  |  | 0.02 |
|  | No | 212 (84.8) | 151 (92.6) |  |
|  | Yes | 38 (15.2) | 12 (7.4) |  |
|  | Missing | 11 | 0 |  |
| Ascites, N (%) | |  |  | 0.36 |
|  | No | 202 (80.5) | 137 (84.0) |  |
|  | Yes | 49 (19.5) | 26 (16.0) |  |
|  | Missing | 10 | 0 |  |
| Biological parameter at the beginning of L2 | |  |  |  |
| Neutrophils, median [IQR], mm3 | | 3944.0 [2760.0 - 5527.0] | 4674.5 [3210.0 - 6571.0] | 0.02 |
|  | Missing | 42 | 25 |  |
| Lymphocytes, median [IQR], mm3 | | 1260.0 [901.0 - 1723.5] | 1300.0 [900.0 - 1871.0] | 0.27 |
|  | Missing | 49 | 38 |  |
| Neutrophil-to-lymphocyte ratio, median [IQR] | | 3.1 [2.2 - 4.9] | 3.5 [2.1 - 5.8] | 0.48 |
|  | Missing | 51 | 38 |  |
| CA19-9, median [IQR], UI/mL | | 654.0 [73.3 - 3851.0] | 1100.0 [194.0 - 10000.0] | 0.02 |
|  | Missing | 57 | 14 |  |
| Treatment | |  |  |  |
| Primary tumor resection, N (%) | |  |  | <0.001 |
|  | Yes | 178 (68.2) | 140 (87.5) |  |
|  | No | 83 (31.8) | 20 (12.5) |  |
|  | Missing | 0 | 3 |  |
| Type of L1 regimen, N (%) | |  |  | <0.001 |
|  | 5-FU ± Oxaliplatin and/or Irinotecan | 76 (29.1) | 93 (57.1) |  |
|  | FOLFIRINOX‡ | 51 (19.6) | 68 (41.8) |  |
|  | FOLFOX§ | 12 (4.6) | 17 (10.4) |  |
|  | FOLFIRI|| or FOLFIRI 3 | 10 (3.8) | 1 (0.6) |  |
|  | 5-FU | 3 (1.1) | 0 (0.0) |  |
|  | 5-FU and nab-paclitaxel | 0 (0.0) | 7 (4.3) |  |
|  | Gemcitabine based | 185 (70.9) | 70 (42.9) |  |
|  | Gemcitabine alone | 132 (50.6) | 54 (33.1) |  |
|  | Gemcitabine and oxaliplatin | 19 (7.3) | 9 (5.5) |  |
|  | Gemcitabine and nab-paclitaxel | 0 (0.0) | 6 (3.7) |  |
|  | Gemcitabine and other therapy¶ | 34 (13.0) | 1 (0.6) |  |
| RECIST Best response in L1, N (%) | |  |  | 0.006 |
|  | Complete or partial response or stability | 170 (67.5) | 130 (79.8) |  |
|  | Progression disease | 82 (32.5) | 33 (20.2) |  |
|  | Missing | 9 | 0 |  |
| Duration of L1, median [IQR], months | | 5.7 [2.9 - 8.7] | 6.2 [3.0 - 11.5] | 0.19 |
| Reason for discontinuation in L1, N (%) | |  |  | <0.001 |
|  | Progression disease | 176 (67.4) | 141 (87.0) |  |
|  | Toxicity | 15 (5.8) | 10 (6.2) |  |
|  | Other | 70 (26.8) | 11 (6.8) |  |
|  | Missing | 0 | 1 |  |
| Type of L2 regimen, N (%) | |  |  | **<**0.001 |
|  | 5-FU ± Oxaliplatin and/or Irinotecan | 204 (78.2) | 84 (51.5) |  |
|  | FOLFIRINOX‡ | 20 (7.7) | 2 (1.2) |  |
|  | FOLFOX§ | 111 (42.5) | 52 (31.9) |  |
|  | FOLFIRI|| or FOLFIRI 3 | 37 (14.2) | 21 (12.9) |  |
|  | 5-FU | 5 (1.9) | 3 (1.8) |  |
|  | Capecitabine | 19 (7.3) | 0 (0.0) |  |
|  | Other therapy# | 12 (4.6) | 6 (3.7) |  |
|  | Gemcitabine based | 57 (21.8) | 79 (48.5) |  |
|  | Gemcitabine alone | 50 (19.2) | 69 (42.4) |  |
|  | Gemcitabine and oxaliplatin | 5 (1.9) | 2 (1.2) |  |
|  | Gemcitabine and nab-paclitaxel | 0 (0.0) | 1 (0.6) |  |
|  | Gemcitabine and other therapy\*\* | 2 (0.7) | 7 (4.3) |  |
|  | Third-line chemotherapy, N (%) |  |  | 0.50 |
|  | Yes | 115 (44.1) | 63 (40.6) |  |
|  | No | 146 (55.9) | 92 (59.4) |  |
|  | Missing | 0 | 8 |  |
| Median OS time [IQR], months | | 5.7 [4.7 – 6.9] | 5.3 [4.5 – 6.2] | 0.13 |
| Median follow-up time (95% CI), months | | All patients were followed until death (maximum time observed = 126.1) except 14 censored patients with a median follow-up equal to 14.1 | 14.7 (12.1 – 31.5) |  |

\*χ2 tests or Fisher’s exact tests used to compare proportions, and Wilcoxon tests used to compare continuous variables between the groups with or without second-line chemotherapy administration. All statistical tests were two-sided. Abbreviations: IQR=Interquartile Range, CI = confidence interval, WHO=World Health Organization, CA 19-9=Carbohydrate Antigen 19-9, 5-FU=5-Fluorouracil, L1=first-line chemotherapy, L2=second-line chemotherapy

†corresponding to prescription of morphine

‡FOLFIRINOX=5-fluorouracil [5-FU], irinotecan, and oxaliplatin

§FOLFOX=5-fluorouracil [5FU], and oxaliplatin

||FOLFIRI=5-fluorouracil [5FU], and irinotecan

¶Other therapy combined with gemcitabine in L1: masitinib (N=12), AM6479 (N=8), capecitabine (N=6), erlotinib (N=4), antiTGFβ (N=3), dasatinib (N=1), TH302 (N=1)

#Other therapy combined with gemcitabine in L2: ERY001 (N=7), capecitabine (N=1), erlotinib (N=1)

\*\*Other therapy classified as 5-FU based in L2: paclitaxel alone (N=6), erlotinib alone (N=6), 5-FU and cisplatin (N=3), raltitrexed and oxaliplatin (N=1), carboplatin and etoposide (N=1), tegafur and uracil (N=1)

The external validation cohort differed from the development cohort in the following respects, stages, jaundice, neutrophils, CA19-9, primary tumor resection, type of first-line regimen, RECIST best response in first-line chemotherapy, reason for discontinuation in first-line chemotherapy, and type of second-line regimen.

The number of events in the external validation cohort was in accordance with recent methodological recommendations (2).

**Supplementary Table 2. Stratified univariate analysis and random univariate analysis of factors associated with overall survival**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameters** | **No. of Patients** | **No. of Events** | **Stratified univariate analysis (OS)** | | **Random univariate analysis (OS)** | |
| **HR (95% CI)** | **P\*** | **HR (95% CI)** | **P\*** |
| Demographic parameters |  |  |  |  |  |  |
| Age in years | 261 | 247 | 1.02 (1.00 - 1.03) | 0.02 | 1.02 (1.00 - 1.03) | 0.02 |
| Sex |  |  |  |  |  |  |
| Male | 158 | 152 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Female | 103 | 95 | 0.79 (0.61 - 1.03) | 0.08 | 0.80 (0.62 - 1.04) | 0.09 |
| Smoking status |  |  |  |  |  |  |
| Never smoker or former smoker | 200 | 187 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Current smoker | 60 | 59 | 1.43 (1.05 - 1.95) | 0.02 | 1.46 (1.08 - 1.98) | 0.01 |
| Missing | 1 | 1 |  |  |  |  |
| Personal history of cancer |  |  |  |  |  |  |
| No | 210 | 197 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 49 | 48 | 1.17 (0.85 - 1.60) | 0.34 | 1.16 (0.84 - 1.59) | 0.37 |
| Missing | 2 | 2 |  |  |  |  |
| Family history of cancer |  |  |  |  |  |  |
| No | 146 | 138 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 113 | 107 | 0.85 (0.66 - 1.09) | 0.20 | 0.85 (0.66 - 1.10) | 0.21 |
| Missing | 2 | 0 |  |  |  |  |
| Family history of pancreatic cancer |  |  |  |  |  |  |
| No | 240 | 227 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 19 | 18 | 1.10 (0.67 - 1.82) | 0.71 | 1.14 (0.71 - 1.85) | 0.59 |
| Missing | 2 | 2 |  |  |  |  |
| Pathologic parameters at diagnosis of cancer |  |  |  |  |  |  |
| Primary tumor site |  |  |  |  |  |  |
| Head | 152 | 142 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Body and/or Tail | 106 | 102 | 1.24 (0.96 - 1.61) | 0.10 | 1.24 (0.96 - 1.60) | 0.10 |
| Missing | 3 | 3 |  |  |  |  |
| Primary tumor size, mm | 242 | 229 | 1.01 (1.00 - 1.01) | 0.16 | 1.01 (1.00- 1.01) | 0.17 |
| Missing | 19 | 18 |  |  |  |  |
| Histological grade |  |  |  |  |  |  |
| Well or moderately differentiated | 100 | 92 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Poorly differentiated or undifferentiated | 28 | 26 | 1.31 (0.84 - 2.04) | 0.24 | 1.32 (0.84 - 2.05) | 0.22 |
| Missing | 133 | 129 |  |  |  |  |
| Stages |  |  |  |  |  |  |
| Localized | 66 | 61 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Locally advanced | 61 | 57 | 1.07 (0.74 - 1.55) | <0.001 | 1.10 (0.76 - 1.59) | <0.001 |
| Metastatic | 134 | 129 | 1.73 (1.26 - 2.37) |  | 1.73 (1.27 - 2.37) |  |
| Tumor extension at the beginning of L2 |  |  |  |  |  |  |
| Number of metastatic sites |  |  |  |  |  |  |
| 0 - 1 | 162 | 152 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| ≥ 2 | 99 | 95 | 1.72 (1.33 - 2.24) | <0.001 | 1.71 (1.32 - 2.21) | <0.001 |
| Lymph node metastases |  |  |  |  |  |  |
| No | 240 | 230 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 21 | 17 | 0.77 (0.47 - 1.27) | 0.30 | 0.76 (0.46 - 1.25) | 0.28 |
| Liver metastases |  |  |  |  |  |  |
| No | 106 | 100 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 155 | 147 | 1.74 (1.34 - 2.26) | <0.001 | 1.74 (1.34 - 2.25) | <0.001 |
| Peritoneal metastases |  |  |  |  |  |  |
| No | 162 | 148 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 99 | 99 | 1.64 (1.26 - 2.12) | <0.001 | 1.62 (1.26 - 2.10) | <0.001 |
| Lung metastases |  |  |  |  |  |  |
| No | 204 | 193 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 57 | 54 | 0.87 (0.43 - 1.76) | 0.70 | 0.95 (0.70 - 1.28) | 0.72 |
| Bone metastases |  |  |  |  |  |  |
| No | 252 | 239 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 9 | 8 | 0.89 (0.44 - 1.80) | 0.74 | 0.85 (0.42 - 1.73) | 0.66 |
| Other metastases |  |  |  |  |  |  |
| No | 257 | 243 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 4 | 4 | 1.12 (0.413 - 3.020) | 0.83 | 1.13 (0.42 - 3.06) | 0.81 |
| Isolated lung metastases |  |  |  |  |  |  |
| No | 248 | 235 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 13 | 12 | 0.5 (0.265 - 0.900) | 0.02 | 0.56 (0.29 - 0.94) | 0.03 |
| Clinical parameters at the beginning of L2 |  |  |  |  |  |  |
| Performance status (WHO) |  |  |  |  |  |  |
| 0 | 47 | 40 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| 1 | 118 | 115 | 2.10 (1.44 - 3.06) |  | 2.01 (1.39 - 2.90) |  |
| ≥ 2 | 86 | 83 | 4.88 (3.26 - 7.32) | <0.001 | 4.62 (3.12 - 6.86) | <0.001 |
| Missing | 10 | 9 |  |  |  |  |
| Body mass index, kg/m2 | 260 | 247 | 0.98 (0.95 - 1.02) | 0.32 | 0.98 (0.95 - 1.02) | 0.32 |
| Missing | 1 | 0 |  |  |  |  |
| Body mass index, kg/m2 |  |  |  |  |  |  |
| Normal weight [18,5-25[ | 167 | 160 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Underweight <18,5 | 39 | 36 | 1.20 (0.83 - 1.72) |  | 1.19 (0.83 - 1.71) |  |
| Overweight [25-30[ and Obesity ≥30 | 54 | 51 | 0.91 (0.66 - 1.26) | 0.47 | 0.91 (0.66 - 1.25) | 0.48 |
| Missing | 1 | 0 |  |  |  |  |
| Pain† |  |  |  |  |  |  |
| No | 119 | 109 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 131 | 128 | 1.91 (1.47 - 2.49) | <0.001 | 1.88 (1.45 - 2.44) | <0.001 |
| Missing | 11 | 10 |  |  |  |  |
| Jaundice |  |  |  |  |  |  |
| No | 212 | 200 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 38 | 37 | 2.59 (1.80 - 3.74) | <0.001 | 2.60 (1.81 - 3.74) | <0.001 |
| Missing | 11 | 10 |  |  |  |  |
| Ascites |  |  |  |  |  |  |
| No | 202 | 190 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 49 | 48 | 2.23 (1.61 - 3.09) | <0.001 | 2.23 (1.61 - 3.09) | <0.001 |
| Missing | 10 | 9 |  |  |  |  |
| Biological parameters at the beginning of L2 |  |  |  |  |  |  |
| Hemoglobin, g/dL | 233 | 223 | 0.83 (0.76 - 0.910) | <0.001 | 0.83 (0.76 - 0.90) | <0.001 |
| Missing | 28 | 24 |  |  |  |  |
| Neutrophils, mm3 (square root value) | 219 | 210 | 1.02 (1.01 - 1.02) | <0.001 | 1.02 (1.01 - 1.02) | <0.001 |
| Missing | 42 | 37 |  |  |  |  |
| Lymphocytes, mm3 (inverse transformation value) | 212 | 204 | 4.7E131 (3.943E25 - 5.6E237) | 0.02 | 8.25E130 (3.157E25 - 2.16E236) |  |
| Missing | 49 | 43 |  |  |  |  |
| Neutrophil-to-lymphocyte ratio (square root value) | 210 | 202 | 1.70 (1.44 - 2.00) | <0.001 | 1.68 (1.43 - 1.97) | <0.001 |
| Missing | 51 | 45 |  |  |  |  |
| Platelets, mm3 (log value) | 230 | 220 | 1.62 (0.91 - 2.89) | 0.10 | 1.64 (0.93 - 2.91) | 0.09 |
| Missing | 31 | 27 |  |  |  |  |
| Creatinine, µmol/L (log value) | 247 | 234 | 0.78 (0.26 - 2.35) | 0.66 | 0.78 (0.26 - 2.34) | 0.65 |
| Missing | 14 | 13 |  |  |  |  |
| Total bilirubin, µmol/L (square root value) | 218 | 209 | 1.16 (1.10 - 1.23) | <0.001 | 1.16 (1.10 - 1.23) | <0.001 |
| Missing |  |  |  |  |  |  |
| Albumin, g/L | 161 | 155 | 0.93 (0.91 - 0.95) | <0.001 | 0.93 (0.91 - 0.96) | <0.001 |
| Missing | 100 | 92 |  |  |  |  |
| CA19-9, UI/mL (square root value) | 204 | 195 | 1.01 (1.01 - 1.01) | <0.001 | 1.01 (1.01 - 1.01) | <0.001 |
| Missing | 57 | 52 |  |  |  |  |
| CEA, ng/mL (log value) | 159 | 150 | 1.87 (1.47 - 2.38) | <0.001 | 1.85 (1.46 - 2.35) | <0.001 |
| Missing | 102 | 97 |  |  |  |  |
| Previous treatment at the beginning of L2 |  |  |  |  |  |  |
| Primary tumor resection |  |  |  |  |  |  |
| Yes | 83 | 76 | 1 |  |  | 1 |
| No | 178 | 171 | 1.57 (1.19 - 2.07) | 0.002 | 1.54 (1.17 - 2.03) | 0.002 |
| Adjuvant chemotherapy |  |  |  |  |  |  |
| Yes | 67 | 61 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| No | 194 | 186 | 1.58 (1.18 - 2.13) | 0.003 | 1.56 (1.16 - 2.09) | 0.003 |
| Radiotherapy |  |  |  |  |  |  |
| Yes | 17 | 15 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| No | 244 | 232 | 1.18 (0.695 - 1.989) | 0.55 | 1.15 (0.681 - 1.940) | 0.60 |
| Neo-adjuvant chemotherapy |  |  |  |  |  |  |
| Yes | 3 | 3 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| No | 258 | 244 | 0.92 (0.292 - 2.887) | 0.88 | 0.93 (0.298 - 2.932) | 0.91 |
| Biliary stent |  |  |  |  |  |  |
| Yes | 83 | 78 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| No | 177 | 168 | 0.85 (0.651 - 1.121) | 0.25 | 0.86 (0.656 - 1.126) | 0.27 |
| Duodenal stent |  |  |  |  |  |  |
| Yes | 19 | 18 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| No | 241 | 228 | 0.81 (0.50 - 1.31) | 0.40 | 0.81 (0.50 - 1.32) | 0.40 |
| Missing | 1 | 1 |  |  |  |  |
| Alcohol celiac plexus |  |  |  |  |  |  |
| Yes | 22 | 21 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| No | 238 | 225 | 0.77 (0.49 - 1.20) | 0.25 | 0.76 (0.48 - 1.20) | 0.24 |
| Missing | 1 | 1 |  |  |  |  |
| First-line chemotherapy |  |  |  |  |  |  |
| Type of L1 regimen |  |  |  |  |  |  |
| 5-FU ± Oxaliplatin and/or Irinotecan | 76 | 69 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Gemcitabine based | 185 | 178 | 1.55 (1.10 - 2.19) | 0.01 | 1.48 (1.06 - 2.08) | 0.02 |
| Number of cures | 261 | 247 | 0.99 (0.98 – 1.00) | 0.01 | 0.99 (0.98 - 1.00) | 0.01 |
| RECIST Best response |  |  |  |  |  |  |
| Complete or partial response or stability | 170 | 161 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Progression disease | 82 | 77 | 1.39 (1.06 - 1.83) | 0.02 | 1.38 (1.05 - 1.81) | 0.02 |
| Missing | 9 | 9 |  |  |  |  |
| Duration of L1 (log value), months | 261 | 247 | 0.52 (0.36 - 0.73) | <0.001 | 0.53 (0.37 - 0.74) | <0.001 |
| Toxicity of grade 3 and 4 |  |  |  |  |  |  |
| No | 198 | 189 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 63 | 58 | 0.77 (0.57 - 1.05) | 0.10 | 0.80 (0.59 - 1.08) | 0.14 |
| Type of toxicity |  |  |  |  |  |  |
| Digestive | 8 | 7 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Neurological | 17 | 14 | 1.02 (0.38 - 2.70) |  | 0.96 (0.39 - 2.39) |  |
| Skin | 4 | 4 | 2.62 (0.70 - 9.84) |  | 2.29 (0.65 - 8.05) |  |
| Hematology | 20 | 20 | 1.91 (0.75 - 4.86) |  | 1.73 (0.72 - 4.12) |  |
| Other | 14 | 13 | 1.89 (0.70 - 5.16) | 0.24 | 1.70 (0.67 - 4.32) | 0.30 |
| Missing | 198 | 189 |  |  |  |  |
| Reason for discontinuation |  |  |  |  |  |  |
| Other | 70 | 61 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Toxicity | 15 | 15 | 1.33 (0.75 - 2.35) |  | 1.29 (0.73 - 2.27) |  |
| Progression disease | 176 | 171 | 1.68 (1.25 - 2.27) | 0.003 | 1.62 (1.21 - 2.18) | 0.005 |
| Locoregional progression |  |  |  |  |  |  |
| No | 207 | 196 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 54 | 51 | 0.91 (0.67 - 1.25) | 0.56 | 0.91 (0.63 - 1.24) | 0.54 |
| Metastatic progression |  |  |  |  |  |  |
| No | 67 | 61 | 1.00 (Reference) |  | 1.00 (Reference) |  |
| Yes | 194 | 186 | 1.50 (1.12 - 2.02) | 0.007 | 1.49 (1.11 - 2.00) | 0.008 |

\*Cox-proportional-hazard models used to estimate association of the parameters with overall survival. Values of P<0.05 were considered statistically significant and all tests were two-sided. Abbreviations: HR=Hazard Ratio, CI=confidence interval, WHO=World Health Organization, CA 19-9=Carbohydrate Antigen 19-9, CEA=Carcinoembryonic Antigen, 5-FU=5-Fluorouracil, L1=first-line chemotherapy, L2=second-line chemotherapy

†corresponding to prescription of morphine

# **Supplementary Table 3. Stratified multivariate analysis and random multivariate analysis of factors associated with overall survival without biological parameters (N = 248)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameters** | | **No. of Patients** | | **No. of Events** | | **Stratified multivariate analysis (OS)** | | | **Random multivariate analysis (OS)** | |
| **HR (95% CI)** | | **P\*** | **HR (95% CI)** | **P\*** |
| Demographic parameters | | |  | |  | |  |  |  |  |
| Age, y | | | 248 | | 235 | | 1.02 (1.00 - 1.04) | 0.02 | 1.02 (1.00 - 1.04) | 0.02 |
| Smoking status | | |  | |  | |  |  |  |  |
|  | Never smoker or former smoker | | 190 | | 178 | | 1.00 (Reference) |  | 1.00 (Reference) |  |
|  | Current smoker | | 58 | | 57 | | 1.45 (1.05 - 2.01) | 0.02 | 1.50 (1.09 - 2.06) | 0.01 |
| Tumor extension at the beginning of L2 | | |  | |  | |  |  |  |  |
| Liver metastases | | |  | |  | |  |  |  |  |
|  | No | | 99 | | 93 | | 1.00 (Reference) |  | 1.00 (Reference) |  |
|  | Yes | | 149 | | 142 | | 2.17 (1.64 - 2.89) | <0.001 | 2.14 (1.62 - 2.84) | <0.001 |
| Clinical parameters at the beginning of L2 | | |  | |  | |  |  |  |  |
| Performance status (WHO) | | |  | |  | |  |  |  |  |
|  | 0 | | 47 | | 40 | | 1.00 (Reference) |  | 1.00 (Reference) |  |
|  | 1 | | 117 | | 114 | | 1.67 (1.13 - 2.49) |  | 1.61 (1.10 - 2.37) |  |
|  | ≥ 2 | | 84 | | 81 | | 3.21 (2.01 - 5.11) | <0.001 | 3.05 (1.93 - 4.81) | <0.001 |
| Pain† | | |  | |  | |  |  |  |  |
|  | No | | 119 | | 109 | | 1.00 (Reference) |  | 1.00 (Reference) |  |
|  | Yes | | 131 | | 128 | | 1.45 (1.09 - 1.93) | 0.01 | 1.41 (1.06 - 1.88) | 0.02 |
| Jaundice | | |  | |  | |  |  |  |  |
|  | No | | 210 | | 198 | | 1.00 (Reference) |  | 1.00 (Reference) |  |
|  | Yes | | 38 | | 37 | | 1.94 (1.31 - 2.89) | 0.001 | 1.96 (1.33 - 2.89) | <0.001 |
| Ascites | | |  | |  | |  |  |  |  |
|  | No | | 200 | | 188 | | 1.00 (Reference) |  | 1.00 (Reference) |  |
|  | Yes | | 48 | | 47 | | 1.74 (1.23 - 2.47) | 0.002 | 1.78 (1.25 - 2.52) | 0.001 |
| Treatment | | |  | |  | |  |  |  |  |
| Duration of L1 (log value), months | | | 248 | | 235 | | 0.48 (0.32 - 0.70) | <0.001 | 0.48 (0.330 - 0.71) | <0.001 |

\*Cox-proportional-hazard models used to estimate association of the parameters with overall survival. Values of P<0.05 were considered statistically significant and all tests were two-sided. Abbreviations: HR=Hazard Ratio, CI=confidence interval, WHO=World Health Organization, 5-FU=5-Fluorouracil, L1=first-line chemotherapy, L2=second-line chemotherapy.

†Corresponding to prescription of morphine.

**Supplementary Table 4. Multivariate analysis of factors associated with overall survival with full-model (N = 230)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameters** | **No. of Patients** | **No. of Events** | **HR (95% CI)** | **P\*** |
| Demographic parameters |  |  |  |  |
| Age in years | 230 | 218 | 1.03 (1.01 - 1.05) | 0.01 |
| Sex |  |  |  |  |
| Male | 138 | 134 | 1.00 (Reference) |  |
| Female | 92 | 84 | 1.13 (0.81 - 1.57) | 0.49 |
| Smoking status |  |  |  |  |
| Never smoker or former smoker | 178 | 167 | 1.00 (Reference) |  |
| Current smoker | 52 | 51 | 1.79 (1.21 - 2.66) | 0.004 |
| Personal history of cancer |  |  |  |  |
| No | 189 | 178 | 1.00 (Reference) |  |
| Yes | 41 | 40 | 0.90 (0.60 - 1.37) | 0.63 |
| Family history of cancer |  |  |  |  |
| No | 128 | 122 | 1.00 (Reference) |  |
| Yes | 102 | 96 | 0.87 (0.62 - 1.23) | 0.44 |
| Family history of pancreatic cancer |  |  |  |  |
| No | 214 | 203 | 1.00 (Reference) |  |
| Yes | 16 | 15 | 1.64 (0.89 - 3.01) | 0.11 |
| Pathologic parameters at diagnosis of cancer |  |  |  |  |
| Primary tumor site |  |  |  |  |
| Head | 133 | 124 | 1.00 (Reference) |  |
| Body and/or Tail | 97 | 94 | 1.50 (1.07 - 2.11) | 0.02 |
| Primary tumor size, mm | 230 | 218 | 1.00 (0.99 - 1.01) | 0.93 |
| Tumor stage |  |  |  |  |
| Localized | 62 | 58 | 1.00 (Reference) |  |
| Locally advanced | 56 | 52 | 0.67 (0.42 - 1.07) |  |
| Metastatic | 112 | 108 | 0.88 (0.57 - 1.37) | 0.23 |
| Tumor extension at the beginning of L2 |  |  |  |  |
| Number of metastatic sites |  |  |  |  |
| 0 - 1 | 143 | 134 | 1.00 (Reference) |  |
| ≥ 2 | 87 | 84 | 0.93 (0.62 - 1.38) | 0.71 |
| Lymph node metastases |  |  |  |  |
| No | 213 | 204 | 1.00 (Reference) |  |
| Yes | 17 | 14 | 1.05 (0.55 - 2.02) | 0.88 |
| Liver metastases |  |  |  |  |
| No | 92 | 86 | 1.00 (Reference) |  |
| Yes | 138 | 132 | 2.20 (1.40 - 3.43) | <0.001 |
| Bone metastases |  |  |  |  |
| No | 224 | 213 | 1.00 (Reference) |  |
| Yes | 6 | 5 | 0.57 (0.20 - 1.61) | 0.29 |
| Other metastases |  |  |  |  |
| No | 227 | 215 | 1.00 (Reference) |  |
| Yes | 3 | 3 | 0.42 (0.39 - 1.77) | 0.18 |
| Isolated lung metastases |  |  |  |  |
| No | 217 | 206 | 1.00 (Reference) |  |
| Yes | 13 | 12 | 0.83 (0.39 - 1.77) | 0.62 |
| Clinical parameters at the beginning of L2 |  |  |  |  |
| Performance status (WHO) |  |  |  |  |
| 0 | 45 | 38 | 1.00 (Reference) |  |
| 1 | 107 | 104 | 1.38 (0.86 - 2.21) |  |
| ≥ 2 | 78 | 76 | 3.40 (1.96 - 5.91) | <0.001 |
| Body mass index, kg/m2 | 230 | 218 | 0.98 (0.94 - 1.03) | 0.37 |
| Pain† |  |  |  |  |
| No | 109 | 99 | 1.00 (Reference) |  |
| Yes | 121 | 119 | 1.57 (1.09 - 2.25) | 0.01 |
| Jaundice |  |  |  |  |
| No | 194 | 182 | 1.00 (Reference) |  |
| Yes | 36 | 36 | 1.75 (1.13 - 2.71) | 0.01 |
| Ascites |  |  |  |  |
| No | 188 | 177 | 1.00 (Reference) |  |
| Yes | 42 | 41 | 1.70 (1.09 - 2.67) | 0.02 |
| Previous treatment at the beginning of L2 |  |  |  |  |
| Radiotherapy |  |  |  |  |
| Yes | 15 | 13 | 1.00 (Reference) |  |
| No | 215 | 205 | 0.55 (0.26 - 1.13) | 0.10 |
| Neo-adjuvant chemotherapy |  |  |  |  |
| Yes | 3 | 3 | 1.00 (Reference) |  |
| No | 227 | 215 | 3.69 (0.92 - 14.70) | 0.06 |
| Biliary stent |  |  |  |  |
| Yes | 74 | 70 | 1.00 (Reference) |  |
| No | 156 | 148 | 1.02 (0.71 - 1.49) | 0.90 |
| Duodenal stent |  |  |  |  |
| Yes | 16 | 15 | 1.00 (Reference) |  |
| No | 214 | 203 | 0.86 (0.45 - 1.64) | 0.66 |
| Alcohol celiac plexus |  |  |  |  |
| Yes | 21 | 20 | 1.00 (Reference) |  |
| No | 209 | 198 | 0.92 (0.54 - 1.57) | 0.77 |
| First-line chemotherapy |  |  |  |  |
| Duration of L1 (log value), months | 230 | 218 | 0.47 (0.29 - 0.76) | 0.002 |
| Toxicity of grade 3 or 4 |  |  |  |  |
| No | 172 | 165 | 1.00 (Reference) |  |
| Yes | 58 | 53 | 0.95 (0.64 - 1.43) | 0.82 |
| Locoregional progression |  |  |  |  |
| No | 183 | 174 | 1.00 (Reference) |  |
| Yes | 47 | 44 | 1.38 (0.91 - 2.10) | 0.13 |
| Metastatic progression |  |  |  |  |
| No | 55 | 49 | 1.00 (Reference) |  |
| Yes | 175 | 169 | 1.43 (0.90 - 2.26) | 0.13 |
| Second-line chemotherapy |  |  |  |  |
| Type of L2 regimen |  |  |  |  |
| 5 FU ± Oxaliplatin and/or Irinotecan | 179 | 169 | 1.00 (Reference) |  |
| Gemcitabine based | 51 | 49 | 1.74 (1.21 - 2.50) | 0.003 |

\*Cox-proportional-hazard models used to estimate association of the parameters with overall survival. Values of P<0.05 were considered statistically significant and all tests were two-sided. The final multivariate Cox model was obtained by entering all parameters, excepting the parameters identified with a strong correlation. Abbreviations: HR=Hazard Ratio, CI=confidence interval, WHO=World Health Organization, 5-FU=5-Fluorouracil, L1=first-line chemotherapy, L2=second-line chemotherapy

†Corresponding to prescription of morphine

# **Supplementary Table 5. Multivariate analysis of factors associated with overall survival with backward procedure (N = 230)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameters** | **No. of Patients** | | **No. of Events** | **HR (95% CI)** | **P\*** |
| Demographic parameters | |  |  |  |  |
| Age in years | | 230 | 218 | 1.02 (1.01 - 1.04) | 0.01 |
| Smoking status | |  |  |  |  |
| Never smoker or former smoker | | 178 | 167 | 1.00 (Reference) |  |
| Current smoker | | 52 | 51 | 1.67 (1.19 - 2.33) | 0.003 |
| Pathologic parameters at diagnosis of cancer | |  |  |  |  |
| Primary tumor site | |  |  |  |  |
| Head | | 133 | 124 | 1.00 (Reference) |  |
| Body and/or Tail | | 97 | 94 | 1.39 (1.05 - 1.84) | 0.02 |
| Tumor extension at the beginning of L2 | |  |  |  |  |
| Liver metastases | |  |  |  |  |
| No | | 92 | 86 | 1.00 (Reference) |  |
| Yes | | 138 | 132 | 2.24 (1.66 - 3.01) | <0.001 |
| Clinical parameters at the beginning of L2 | |  |  |  |  |
| Performance status (WHO) | |  |  |  |  |
| 0 | | 45 | 38 | 1.00 (Reference) |  |
| 1 | | 107 | 104 | 1.40 (0.94 - 2.11) |  |
| ≥ 2 | | 78 | 76 | 2.76 (1.69 - 4.50) | <0.001 |
| Pain† | |  |  |  |  |
| No | | 109 | 99 | 1.00 (Reference) |  |
| Yes | | 121 | 119 | 1.42 (1.04 - 1.94) | 0.03 |
| Jaundice | |  |  |  |  |
| No | | 194 | 182 | 1.00 (Reference) |  |
| Yes | | 36 | 36 | 2.04 (1.37 - 3.03) | <0.001 |
| Ascites | |  |  |  |  |
| No | | 188 | 177 | 1.00 (Reference) |  |
| Yes | | 42 | 41 | 1.88 (1.30 - 2.72) | <0.001 |
| First-line chemotherapy | |  |  |  |  |
| Duration of L1 (log value), months | | 230 | 218 | 0.52 (0.35 - 0.78) | 0.002 |
| Second-line chemotherapy | |  |  |  |  |
| Type of L2 regimen | |  |  |  |  |
| 5 FU ± Oxaliplatin and/or Irinotecan | | 179 | 169 | 1.00 (Reference) |  |
| Gemcitabine based | | 51 | 49 | 1.72 (1.22 - 2.41) | 0.002 |

\*Cox-proportional-hazard models used to estimate association of the parameters with overall survival. Values of P<0.05 were considered statistically significant and all tests were two-sided. The final multivariate Cox model was obtained by entering all parameters, excepting the parameters identified with a strong correlation, with a backward procedure (threshold of stay set to 0.1 and 0.05). Abbreviations: HR=Hazard Ratio, CI=confidence interval, WHO=World Health Organization, 5-FU=5-Fluorouracil, L1=first-line chemotherapy, L2=second-line chemotherapy

The results were similar with the thresholds of stay set to 0.1 and 0.05.

†Corresponding to prescription of morphine.

**Supplementary Table 6. Multivariate analysis of factors associated with overall survival with stepwise procedure (N = 230)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameters** | | **No. of Patients** | **No. of Events** | **HR (95% CI)** | **P\*** |
| Demographic parameters | |  |  |  |  |
| Age in years | | 230 | 218 | 1.02 (1.01 - 1.04) | 0.01 |
| Smoking status | |  |  |  |  |
|  | Never smoker or former smoker | 178 | 167 | 1.00 (Reference) |  |
|  | Current smoker | 52 | 51 | 1.67 (1.19 - 2.33) | 0.003 |
| Pathologic parameters at diagnosis of cancer | |  |  |  |  |
| Primary tumor site | |  |  |  |  |
|  | Head | 133 | 124 | 1.00 (Reference) |  |
|  | Body and/or Tail | 97 | 94 | 1.39 (1.05 - 1.84) | 0.02 |
| Tumor extension at the beginning of L2 | |  |  |  |  |
| Liver metastases | |  |  |  |  |
|  | No | 92 | 86 | 1.00 (Reference) |  |
|  | Yes | 138 | 132 | 2.24 (1.66 - 3.01) | <0.001 |
| Clinical parameters at the beginning of L2 | |  |  |  |  |
| Performance status (WHO) | |  |  |  |  |
|  | 0 | 45 | 38 | 1.00 (Reference) |  |
|  | 1 | 107 | 104 | 1.40 (0.94 - 2.11) |  |
|  | ≥ 2 | 78 | 76 | 2.76 (1.69 - 4.50) | <0.001 |
| Pain† | |  |  |  |  |
|  | No | 109 | 99 | 1.00 (Reference) |  |
|  | Yes | 121 | 119 | 1.42 (1.04 - 1.94) | 0.03 |
| Jaundice | |  |  |  |  |
|  | No | 194 | 182 | 1.00 (Reference) |  |
|  | Yes | 36 | 36 | 2.04 (1.37 - 3.03) | <0.001 |
| Ascites | |  |  |  |  |
|  | No | 188 | 177 | 1.00 (Reference) |  |
|  | Yes | 42 | 41 | 1.88 (1.30 - 2.72) | <0.001 |
| First-line chemotherapy | |  |  |  |  |
| Duration of L1 (log value), months | | 230 | 218 | 0.52 (0.35 - 0.78) | 0.002 |
| Second-line chemotherapy | |  |  |  |  |
| Type of L2 regimen | |  |  |  |  |
|  | 5 FU ± Oxaliplatin and/or Irinotecan | 179 | 169 | 1.00 (Reference) |  |
|  | Gemcitabine based | 51 | 49 | 1.72 (1.22 - 2.41) | 0.002 |

\*Cox-proportional-hazard models used to estimate association of the parameters with overall survival. Values of P<0.05 were considered statistically significant and all tests were two-sided. Abbreviations: HR=Hazard Ratio, CI=confidence interval, WHO=World Health Organization, 5-FU=5-Fluorouracil, L1=first-line chemotherapy, L2=second-line chemotherapy. The final multivariate Cox model was obtained by entering all parameters, excepting the parameters identified with a strong correlation, with a stepwise procedure (threshold of entry set to 0.25 and threshold of stay set to 0.1 and 0.05). The results were similar with the thresholds of stay set to 0.1 and 0.05.

†corresponding to prescription of morphine

**Supplementary Table 7. Multivariate analysis of factors associated with overall survival with forward procedure (N = 230)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameters** | **No. of Patients** | **No. of Events** | **HR (95% CI)** | **P\*** |
| Demographic parameters |  |  |  |  |
| Age, y | 230 | 218 | 1.02 (1.00 - 1.04) | 0.02 |
| Smoking status |  |  |  |  |
| Never smoker or former smoker | 178 | 167 | 1.00 (Reference) |  |
| Current smoker | 52 | 51 | 1.56 (1.11 - 2.19) | 0.01 |
| Family history of cancer |  |  |  |  |
| No | 128 | 122 | 1.00 (Reference) |  |
| Yes | 102 | 96 | 0.79 (0.58 - 1.08) | 0.14 |
| Family history of pancreatic cancer |  |  |  |  |
| No | 214 | 203 | 1.00 (Reference) |  |
| Yes | 16 | 15 | 1.63 (0.92 - 2.88) | 0.10 |
| Pathologic parameters at diagnosis of cancer |  |  |  |  |
| Primary tumor site |  |  |  |  |
| Head | 133 | 124 | 1.00 (Reference) |  |
| Body and/or Tail | 97 | 94 | 1.39 (1.05 - 1.84) | 0.02 |
| Tumor extension at the beginning of L2 |  |  |  |  |
| Liver metastases |  |  |  |  |
| No | 92 | 86 | 1.00 (Reference) |  |
| Yes | 138 | 132 | 2.09 (1.53 - 2.87) | <0.001 |
| Clinical parameters at the beginning of L2 |  |  |  |  |
| Performance status (WHO) |  |  |  |  |
| 0 | 45 | 38 | 1.00 (Reference) |  |
| 1 | 107 | 104 | 1.46 (0.97 - 2.19) |  |
| ≥ 2 | 78 | 76 | 2.94 (1.80 - 4.83 | <0.001 |
| Pain† |  |  |  |  |
| No | 109 | 99 | 1.00 (Reference) |  |
| Yes | 121 | 119 | 1.52 (1.10 - 2.09) | 0.01 |
| Jaundice |  |  |  |  |
| No | 194 | 182 | 1.00 (Reference) |  |
| Yes | 36 | 36 | 1.92 (1.29 - 2.88) | 0.002 |
| Ascites |  |  |  |  |
| No | 188 | 177 | 1.00 (Reference) |  |
| Yes | 42 | 41 | 1.80 (1.23 - 2.62) | 0.003 |
| First-line chemotherapy |  |  |  |  |
| Duration of L1 (log value), months | 230 | 218 | 0.51 (0.34 - 0.76) | 0.001 |
| Metastatic progression |  |  |  |  |
| No | 55 | 49 | 1.00 (Reference) |  |
| Yes | 175 | 169 | 1.26 (0.88 - 1.80) | 0.22 |
| Second-line chemotherapy |  |  |  |  |
| Type of L2 regimen |  |  |  |  |
| 5 FU ± Oxaliplatin and/or Irinotecan | 179 | 169 | 1.00 (Reference) |  |
| Gemcitabine based | 51 | 49 | 1.77 (1.25 - 2.49) | 0.001 |

\*Cox-proportional-hazard models used to estimate association of the parameters with overall survival. Values of P<0.05 were considered statistically significant and all tests were two-sided. Abbreviations: HR=Hazard Ratio, CI=confidence interval, WHO=World Health Organization, 5-FU=5-Fluorouracil, L1=first-line chemotherapy, L2=second-line chemotherapy. The final multivariate Cox model was obtained by entering all parameters, excepting the parameters identified with a strong correlation, with a forward procedure (threshold of entry set to 0.25).

†Corresponding to prescription of morphine

# **Supplementary Table 8. Multivariate analysis of “pragmatic parameters” frequently used in multidisciplinary meeting, associated with overall survival (N = 248)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameters** | | **No. of Patients** | **No. of Events** | **HR (95% CI)** | **P\*** |
| Age, y | | 248 | 235 | 1.01 (0.99 - 1.02) | 0.52 |
| Performance status (WHO) | |  |  |  |  |
|  | 0 | 47 | 40 | 1.00 (reference) |  |
|  | 1 | 117 | 114 | 1.86 (1.28 - 2.69) |  |
|  | ≥ 2 | 84 | 81 | 4.16 (2.78 - 6.22) | <0.001 |
| Duration of L1 (log value), months | | 248 | 235 | 0.57 (0.39 - 0.84) | 0.004 |
|  | | | | | |

\*Cox-proportional-hazard models used to estimate association of the parameters with overall survival. Values of P<0.05 were considered statistically significant and all tests were two-sided. Abbreviations: HR=Hazard Ratio, CI=confidence interval, WHO=World Health Organization, L1=first-line of chemotherapy.

# **Supplementary Table 9. Patient characteristics with second-line chemotherapy administration, according to prognostic score groups**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | | **Patients not eligible to score** | **Patients eligible to score** |  | **High risk group** | **Intermediate risk group** | **Low risk group** |  |
| **(N = 13** | **(N = 248)** | **P\*** | **(N = 31)** | **(N = 94)** | **(N = 123)** | **P\*** |
| Age, median [IQR], y | | 61.5 [56.0 - 76.2] | 65.8 [60.5 - 72.8] | 0.49 | 69.4 [63.7 - 74.9] | 65.3 [59.7 - 73.5] | 65.8 [60.3 - 72.1] | 0.18 |
| Smoking status, N (%) | |  |  | 0.74 |  |  |  | <0.001 |
|  | Never smoker or former smoker | 10 (83.3) | 190 (76.6) |  | 20 (64.5) | 61 (64.9) | 109 (88.6) |  |
|  | Current smoker | 2 (16.7) | 58 (23.4) |  | 11 (35.5) | 33 (35.1) | 14 (11.4) |  |
|  | Missing | 1 | 0 |  | 0 | 0 |  |  |
| Liver metastases, N (%) | |  |  | 0.32 |  |  |  | <0.001 |
|  | No | 7 (53.9) | 99 (39.9) |  | 0 (0.0) | 23 (24.5) | 76 (61.8) |  |
|  | Yes | 6 (46.1) | 149 (60.1) |  | 31 (100.0) | 71 (75.5) | 47 (38.2) |  |
| Performance status (WHO), N (%) | |  |  | 0.59 |  |  |  | <0.001 |
|  | 0 | 0 (0.0) | 47 (18.9) |  | 0 (0.0) | 2 (2.1) | 45 (36.6) |  |
|  | 1 | 1 (33.3) | 117 (47.2) |  | 0 (0.0) | 50 (53.2) | 67 (54.5) |  |
|  | ≥ 2 | 2 (66.7) | 84 (33.9) |  | 31 (100.0) | 42 (44.7) | 11 (8.9) |  |
|  | Missing | 10 | 0 |  | 0 | 0 |  |  |
| Pain†, N (%) | |  |  | 1.00 |  |  |  | <0.001 |
|  | No | 1 (50.0) | 118 (47.6) |  | 6 (19.3) | 33 (35.1) | 79 (64.2) |  |
|  | Yes | 1 (50.0) | 130 (52.4) |  | 25 (80.7) | 61 (64.9) | 44 (35.8) |  |
|  | Missing | 11 | 0 |  | 0 | 0 |  |  |
| Jaundice, N (%) | |  |  | 1.00 |  |  |  | <0.001 |
|  | No | 2 (100.0) | 210 (84.7) |  | 12 (38.7) | 76 (80.9) | 122 (99.2) |  |
|  | Yes | 0 (0.0) | 38 (15.3) |  | 19 (61.3) | 18 (19.1) | 1 (0.8) |  |
|  | Missing | 11 | 0 |  | 0 | 0 |  |  |
| Ascites, N (%) | |  |  | 0.48 |  |  |  | <0.001 |
|  | No | 2 (66.7) | 200 (80.7) |  | 14 (45.2) | 71 (75.5) | 115 (93.5) |  |
|  | Yes | 1 (33.3) | 48 (19.3) |  | 17 (54.8) | 23 (24.5) | 8 (6.5) |  |
|  | Missing | 10 | 0 |  | 0 | 0 |  |  |
| Duration of L1, median [IQR], months | | 4.1 [2.3 - 6.6] | 5.7 [2.9 - 8.7] | 0.29 | 2.9 [2.2 - 5.6] | 3.9 [2.7 - 7.3] | 7.4 [4.0 - 10.3] | <0.001 |
| Type of L2 regimen, N (%) | |  |  | 0.49 |  |  |  | 0.006 |
|  | Gemcitabine based | 4 (30.8) | 53 (21.4) |  | 9 (29.0) | 28 (29.8) | 16 (13.0) |  |
|  | 5-FU ± Oxaliplatin and/or Irinotecan | 9 (69.2) | 195 (78.6) |  | 22 (71.0) | 66 (70.2) | 107 (87.0) |  |
| Median OS time [IQR], months | | 3.0 [1.9 - 6.3] | 6.0 [4.7 – 7.2] | 0.09 | 1.4 [1.2 – 1.7] | 3.6 [2.6 - 4.7] | 11.3 [9.1 – 12.9] | <0.001 |
|  | | | | | | | | |

\*χ2 tests or Fisher’s exact tests used to compare proportions, and Wilcoxon tests used to compare continuous variables between the groups with or without second-line chemotherapy administration. All statistical tests were two-sided. Abbreviations: IQR=interquartile range, WHO=World Health Organization, 5-FU=5-Fluorouracil, L1=first-line chemotherapy, L2=second-line chemotherapy.

†Corresponding to prescription of morphine.

# **Supplementary Table 10. Patient characteristics according to prognostic score groups, according to second-line chemotherapy administration**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | | **High risk group** | | | **Intermediate risk group** | | | **Low risk group** | | |
| **Second-line chemotherapy administration** | **No second-line chemotherapy administration** | **P\*** | **Second-line chemotherapy administration** | **No second-line chemotherapy administration** | **P\*** | **Second-line chemotherapy administration** | **No second-line chemotherapy administration** | **P\*** |
| **(N = 31)** | **(N = 8)** | **(N = 94)** | **(N = 32)** | **(N = 123)** | **(N = 37)** |
| Age, median [IQR], years | | 69.4 [63.7 - 74.9] | 72.9 [60.4 - 74.6] | 0.97 | 65.3 [59.7 - 73.5] | 75.8 [66.0 - 79.7] | <0.001 | 65.8 [60.3 - 72.1] | 70.3 [61.8 - 75.5] | 0.04 |
| Smoking status, N (%) | |  |  | 0.57 |  |  | 0.69 |  |  | 0.27 |
|  | Never smoker or former smoker | 20 (64.5) | 6 (75.0) |  | 61 (64.9) | 22 (68.8) |  | 109 (88.6) | 30 (81.1) |  |
|  | Current smoker | 11 (35.5) | 2 (25.0) |  | 33 (35.1) | 10 (31.2) |  | 14 (11.4) | 7 (18.9) |  |
| Liver metastases, N (%) | |  |  | - |  |  | 0.30 |  |  | 0.03 |
|  | No | 0 (0.0) | 0 (0.0) |  | 23 (24.5) | 5 (15.6) |  | 76 (61.8) | 30 (81.1) |  |
|  | Yes | 31 (100.0) | 8 (100.0) |  | 71 (75.5) | 27 (84.4) |  | 47 (38.2) | 7 (18.9) |  |
| Performance status (WHO), N (%) | |  |  | - |  |  | <0.001 |  |  | <0.001 |
|  | 0 | 0 (0.0) | 0 (0.0) |  | 2 (2.1) | 0 (0.0) |  | 45 (36.6) | 5 (13.5) |  |
|  | 1 | 0 (0.0) | 0 (0.0) |  | 50 (53.2) | 1 (3.1) |  | 67 (54.5) | 6 (16.2) |  |
|  | ≥ 2 | 31 (100.0) | 8 (100.0) |  | 42 (44.7) | 31 (96.9) |  | 11 (8.9) | 26 (70.3) |  |
| Pain†, N (%) | |  |  | 0.17 |  |  | 0.81 |  |  | 0.84 |
|  | No | 6 (19.3) | 4 (50.0) |  | 33 (35.1) | 12 (37.5) |  | 79 (64.2) | 25 (67.6) |  |
|  | Yes | 25 (80.7) | 4 (50.0) |  | 61 (64.9) | 20 (62.5) |  | 44 (35.8) | 12 (32.4) |  |
| Jaundice, N (%) | |  |  | 0.04 |  |  | 0.80 |  |  | 0.04 |
|  | No | 12 (38.7) | 0 (0.0) |  | 76 (80.9) | 25 (78.1) |  | 122 (99.2) | 34 (91.9) |  |
|  | Yes | 19 (61.3) | 8 (100.0) |  | 18 (19.1) | 7 (21.9) |  | 1 (0.8) | 3 (8.1) |  |
| Ascites, N (%) | |  |  | 1.00 |  |  | 0.95 |  |  | 0.18 |
|  | No | 14 (45.2) | 4 (50.0) |  | 71 (75.5) | 24 (75.0) |  | 115 (93.5) | 32 (86.5) |  |
|  | Yes | 17 (54.8) | 4 (50.0) |  | 23 (24.5) | 8 (25.0) |  | 8 (6.5) | 5 (13.5) |  |
| Duration of L1, median [IQR], months | | 2.9 [2.2 - 5.6] | 0.1 [0.1 - 0.6] | <0.001 | 3.9 [2.7 - 7.3] | 1.3 [0.6 - 2.5] | <0.001 | 7.4 [4.0 - 10.3] | 5.7 [3.4 - 10.4] | 0.22 |
| Type of L2 regimen‡, N (%) | |  |  | 0.16 |  |  | 0.22 |  |  | 0.62 |
|  | Gemcitabine based | 9 (29.0) | 0 (0.0) |  | 28 (29.8) | 6 (18.7) |  | 16 (13.0) | 6 (16.2) |  |
|  | 5-FU ± Oxaliplatin and/or Irinotecan | 22 (71.0) | 8 (100.0) |  | 66 (70.2) | 26 (81.3) |  | 107 (87.0) | 31 (83.8) |  |
| Median OS time [IQR], months | | 1.4 [1.1 – 1.7] | 0.4 [0.3 – 0.7] | <0.001 | 3.6 [2.6 – 4.7] | 1.2 [0.6 - 2.1] | <0.001 | 11.3 [9.1 – 12.9] | 2.2 [1.2 – 3.0] | <0.001 |

\*χ2 tests or Fisher’s exact tests used to compare proportions, and Wilcoxon tests used to compare continuous variables between the groups with or without second-line chemotherapy administration. All statistical tests were two-sided. Abbreviations: IQR=interquartile range, WHO=World Health Organization, 5-FU=5-Fluorouracil, L1=first-lien chemotherapy, L2=second-line chemotherapy.

†Corresponding to prescription of morphine

‡A type of regimen was assigned to each patient who did not receive L2 according to the chemotherapy that could have been proposed in multidisciplinary meeting.

# **Supplementary Table 11. Assessment for an interaction between the three risk group and the second-line administration for overall survival prediction**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameters** | **No. of Patients** | **No. of Events** | **P\*** |
| Risk-groups | 325 | 302 | <0.001 |
| L2 administration | 325 | 302 | <0.001 |
| Interaction term for risk group and L2 administration | 325 | 302 | 0.01 |
|  | | | |

\*Cox-proportional-hazard models used to estimate association of the parameters with overall survival. Values of P<0.05 were considered statistically significant and all tests were two-sided. Abbreviations: L2=second-line chemotherapy.

# **Supplementary Table 12. Association of the risk group and the second-line administration with overall survival by combining the two sets of information**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameters** | | **No. of Patients** | **No. of Events** | **HR (95% CI)** | **P\*** |
| Risk group and L2 administration interaction | |  |  |  | <0.001 |
|  | Low risk group with L2 administration | 123 | 114 | 1.00 (Reference) |  |
|  | Low risk group without L2 administration | 37 | 29 | 2.11 (1.40 - 3.18) |  |
|  | Intermediate risk group with L2 administration | 94 | 91 | 2.65 (1.98 - 3.54) |  |
|  | Intermediate risk group without L2 administration | 32 | 30 | 10.13 (6.44 - 15.92) |  |
|  | High risk group with L2 administration | 31 | 30 | 8.40 (5.38 - 13.10) |  |
|  | High risk group without L2 administration | 8 | 8 | 65.40 (28.39 - 150.65) |  |
|  | | | | | |

\*Cox-proportional-hazard models used to estimate association of the parameters with overall survival. Values of P<0.05 were considered statistically significant and all tests were two-sided. Abbreviations: HR=Hazard Ratio, CI=confidence interval, L2=second-line chemotherapy.

**Supplementary Table 13. Multivariate analysis of factors associated with overall survival with biological parameters (N = 178)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameters** | | **No. of Patients** | **No. of Events** | **HR (95% CI)** | **P\*** | **β** | **Points** |
| Demographic parameters | |  |  |  |  |  |  |
| Age, years | | 178 | 172 | 1.02 (1.00 - 1.04) | 0.02 | 0.02194 | 52 |
| Smoking status | |  |  |  |  |  |  |
|  | Never smoker or former smoker | 130 | 125 | 1.00 (Reference) |  |  |  |
|  | Current smoker | 48 | 47 | 1.71 (1.19 - 2.46) | 0.004 | 0.53759 | 23 |
| Tumor extension at the beginning of L2 | |  |  |  |  |  |  |
| Liver metastases | |  |  |  |  |  |  |
|  | No | 103 | 99 | 1.00 (Reference) |  |  |  |
|  | Yes | 75 | 73 | 1.72 (1.22 - 2.42) | 0.002 | 0.53954 | 23 |
| Clinical parameters at the beginning of L2 | |  |  |  |  |  |  |
| Performance status (WHO) | |  |  |  |  |  |  |
|  | 0 | 30 | 27 | 1.00 (Reference) |  |  |  |
|  | 1 | 97 | 94 | 1.60 (1.00 - 2.55) |  | 0.46888 | 20 |
|  | ≥ 2 | 51 | 51 | 2.60 (1.49 - 4.55) | 0.003 | 0.95677 | 42 |
| Pain† | |  |  |  |  |  |  |
|  | No | 85 | 80 | 1.00 (Reference) |  |  |  |
|  | Yes | 93 | 92 | 1.42 (1.00 - 2.01) | 0.05 | 0.34987 | 15 |
| Jaundice | |  |  |  |  |  |  |
|  | No | 152 | 146 | 1.00 (Reference) |  |  |  |
|  | Yes | 26 | 26 | 1.79 (1.09 - 2.93) | 0.02 | 0.58028 | 25 |
| Ascites | |  |  |  |  |  |  |
|  | No | 141 | 135 | 1.00 (Reference) |  |  |  |
|  | Yes | 37 | 37 | 1.57 (1.04 - 2.36) | 0.03 | 0.44942 | 20 |
| Biological parameters at the beginning of L2 | |  |  |  |  |  |  |
| Neutrophil-to-lymphocyte ratio (square root value) | | 178 | 172 | 1.43 (1.15 - 1.76) | 0.001 | 0.35421 | 100 |
| CA19-9, UI/mL (square root value) | | 178 | 172 | 1.0 (1.00 - 1.01) | 0.007 | 0.00331 | 79 |
| Treatment | |  |  |  |  |  |  |
| Duration of L1 (log value), months | | 178 | 172 | 0.53 (0.33 - 0.86) | 0.01 | -0.62690 | 71 |
| Type of L2 regimen | |  |  |  |  |  |  |
|  | 5-FU ± Oxaliplatin and/or Irinotecan | 138 | 133 | 1.00 (Reference) |  |  |  |
|  | Gemcitabine based | 40 | 39 | 1.69 (1.15 - 2.49) | 0.008 | 0.52640 | 23 |

\*Cox-proportional-hazard models used to estimate association of the parameters with overall survival. Values of P<0.05 were considered statistically significant and all tests were two-sided. The final multivariate Cox model was obtained by entering risks factors from the univariate model that achieved p ≤ 0.05 as the thresholds in a single multivariate proportional hazards model. Abbreviations: HR=Hazard Ratio, CI=confidence interval, WHO=World Health Organization, CA 19-9=Carbohydrate Antigen 19-9, 5-FU=5-Fluorouracil, L1=first-line chemotherapy, L2=second-line chemotherapy.

†Corresponding to prescription of morphine.

# **Supplementary Table 14. Stratified multivariate analysis and random multivariate analysis of factors associated with overall survival with biological parameters (N = 178)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameters** | | **No. of Patients** | | **No. of Events** | | **Stratified multivariate analysis (OS)** | | **Random multivariate analysis (OS)** | |
|  | | **HR (95% CI)** | | **P\*** | **HR (95% CI)** | **P\*** |
| Demographic parameters | |  |  | |  | |  |  |  |
| Age, years | | 178 | 172 | | 1.02 (1.00 - 1.04) | | 0.02 | 1.02 (1.00 - 1.04) | 0.02 |
| Smoking status | |  |  | |  | |  |  |  |
|  | Never smoker or former smoker | 130 | 125 | | 1.00 (Reference) | |  | 1.00 (Reference) |  |
|  | Current smoker | 48 | 47 | | 1.66 (1.14 - 2.42) | | 0.009 | 1.72 (1.20 - 2.48) | 0.003 |
| Tumor extension at the beginning of L2 | |  |  | |  | |  |  |  |
| Liver metastases | |  |  | |  | |  |  |  |
|  | No | 103 | 99 | | 1.00 (Reference) | |  | 1.00 (Reference) |  |
|  | Yes | 75 | 73 | | 1.72 (1.22 - 2.43) | | 0.002 | 1.71 (1.21 - 2.41) | 0.002 |
| Clinical parameters at the beginning of L2 | |  |  | |  | |  |  |  |
| Performance status (WHO) | |  |  | |  | |  |  |  |
|  | 0 | 30 | 27 | | 1.00 (Reference) | |  | 1.00 (Reference) |  |
|  | 1 | 97 | 94 | | 1.65 (1.02 - 2.67) | |  | 1.59 (1.00 - 2.52) |  |
|  | ≥ 2 | 51 | 51 | | 2.74 (1.54 - 4.86) | | 0.002 | 2.59 (1.48 - 4.53) | 0.003 |
| Pain† | |  |  | |  | |  |  |  |
|  | No | 85 | 80 | | 1.00 (Reference) | |  | 1.00 (Reference) |  |
|  | Yes | 93 | 92 | | 1.46 (1.03 - 2.06) | | 0.03 | 1.4 (1.00 – 2.00) | 0.05 |
| Jaundice | |  |  | |  | |  |  |  |
|  | No | 152 | 146 | | 1.00 (Reference) | |  | 1.00 (Reference) |  |
|  | Yes | 26 | 26 | | 1.78 (1.08 - 2.94) | | 0.02 | 1.80 (1.10 - 2.94) | 0.02 |
| Ascites | |  |  | |  | |  |  |  |
|  | No | 141 | 135 | | 1.00 (Reference) | |  | 1.00 (Reference) |  |
|  | Yes | 37 | 37 | | 1.51 (1.01 - 2.27) | | 0.05 | 1.54 (1.03 - 2.32) | 0.04 |
| Biological parameters at the beginning of L2 | |  |  | |  | |  |  |  |
| Neutrophil-to-lymphocyte ratio (square root value) | | 178 | 172 | | 1.43 (1.16 - 1.77) | | 0.001 | 1.43 (1.15 - 1.76) | 0.001 |
| CA19-9, UI/mL (square root value) | | 178 | 172 | | 1.00 (1.00 - 1.01) | | 0.007 | 1.00 (1.00 - 1.01) | 0.007 |
| Treatment | |  |  | |  | |  |  |  |
| Duration of L1 (log value), months | | 178 | 172 | | 0.53 (0.33 - 0.86) | | 0.01 | 0.54 (0.34 - 0.87) | 0.01 |

\*Cox-proportional-hazard models used to estimate association of the parameters with overall survival (OS). Values of P<0.05 were considered statistically significant and all tests were two-sided. Abbreviations: HR=Hazard Ratio, CI=confidence interval, WHO=World Health Organization, CA 19-9=Carbohydrate Antigen 19-9, 5-FU=5-Fluorouracil, L1=first-line chemotherapy, L2=second-line chemotherapy.

†Corresponding to prescription of morphine.

# **Supplementary Table 15. Final multivariate model multiple imputation analysis with biological parameters**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Parameters** | **Complete subject analysis** | | | **Multiple imputation analysis** | | |
| **(N = 178)** | | | **(N = 500 imputed dataset)** | | |
| **β** | **SE** | **P\*** | **β** | **SE** | **P\*** |
| Age, years | 0.02194 | 0.00959 | 0.02 | 0.021769 | 0.008005 | 0.007 |
| Smoking status | 0.53759 | 0.18578 | 0.004 | 0.352819 | 0.162989 | 0.03 |
| Liver metastases | 0.53954 | 0.17502 | 0.002 | 0.641621 | 0.148332 | <0.001 |
| Performance status (WHO) | 0.46888 | 0.23751 | 0.05 | 0.396736 | 0.203046 | 0.05 |
| 1 |  |  |  |  |  |  |
| ≥ 2 | 0.95677 | 0.28527 | <0.001 | 0.973159 | 0.243204 | <0.001 |
| Pain† | 0.34987 | 0.17655 | 0.05 | 0.337280 | 0.150524 | 0.03 |
| Jaundice | 0.58028 | 0.25180 | 0.02 | 0.531414 | 0.212001 | 0.01 |
| Ascites | 0.44942 | 0.20832 | 0.03 | 0.479659 | 0.184106 | 0.01 |
| Neutrophil-to-lymphocyte ratio (square root value) | 0.35421 | 0.10759 | 0.001 | 0.326193 | 0.096877 | <0.001 |
| CA19-9, UI/mL (square root value) | 0.00331 | 0.00122 | 0.007 | 0.002606 | 0.001136 | 0.02 |
| Duration of L1 (log value), months | -0.62690 | 0.24436 | 0.01 | -0.462659 | 0.200964 | 0.02 |
| Type of L2 regimen | 0.52640 | 0.19722 | 0.008 | 0.567719 | 0.167135 | <0.001 |

\*Cox-proportional-hazard models used to estimate association of the parameters with overall survival. Values of P<0.05 were considered statistically significant and all tests were two-sided. Abbreviations: SE=standard error, WHO=World Health Organization, CA 19-9=Carbohydrate Antigen 19-9, L1=first-line chemotherapy, L2=second-line chemotherapy

†Corresponding to prescription of morphine

**Supplementary Figures**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Age** | **Smoking status** | **Stages** | **Number of metastatic sites** | **Liver metastases** | **Peritoneal metastases** | **Isolated lung metastases** | **Performance status (WHO)** | **Pain** | **Jaundice** | **Ascites** | **Hemoglobin** | **Neutrophils** | **Lymphocytes** | **Neutrophil-to-lymphocyte ratio** | **Total bilirubin** | **Albumin** | **CA19-9** | **CEA** | **Primary tumor resection** | **Adjuvant chemotherapy** | **First-line chemotherapy** | | | | | **Type of L2 regimen** |
| **Number of cures** | **RECIST Best response** | **Duration of L1** | **Reason for discontinuation** | **Metastatic progression** |
| **Age** | | 1.00000 | -0.14746 | -0.03588 | 0.06591 | -0.07821 | -0.05167 | 0.05491 | 0.14152 | -0.06185 | -0.04516 | -0.09459 | -0.02676 | 0.01379 | 0.01932 | -0.00723 | -0.05639 | -0.05000 | -0.01179 | 0.04026 | 0.07004 | 0.02835 | 0.08083 | 0.06080 | -0.02969 | -0.04457 | -0.03999 | 0.16440 |
|  | |  | 0.0173 | 0.5639 | 0.2888 | 0.2079 | 0.4058 | 0.3769 | 0.0249 | 0.3301 | 0.4772 | 0.1351 | 0.6845 | 0.8392 | 0.7797 | 0.9171 | 0.4074 | 0.5288 | 0.8671 | 0.6143 | 0.2596 | 0.6485 | 0.1930 | 0.3364 | 0.6330 | 0.4734 | 0.5201 | 0.0078 |
|  | | 261 | 260 | 261 | 261 | 261 | 261 | 261 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 261 | 261 | 261 | 252 | 261 | 261 | 261 | 261 |
| **Smoking status** | | -0.14746 | 1.00000 | 0.02516 | -0.03471 | 0.02290 | -0.01591 | 0.00000 | 0.14604 | 0.08743 | -0.02154 | -0.00770 | 0.10802 | 0.06128 | -0.04696 | 0.02644 | -0.01864 | 0.02184 | 0.11684 | 0.04883 | -0.02259 | -0.09312 | -0.11749 | -0.02397 | -0.00369 | 0.00719 | 0.08874 | -0.15106 |
|  | | 0.0173 |  | 0.6863 | 0.5775 | 0.7133 | 0.7985 | 1.0000 | 0.0206 | 0.1682 | 0.7347 | 0.9034 | 0.1000 | 0.3668 | 0.4964 | 0.7032 | 0.7844 | 0.7833 | 0.0961 | 0.5411 | 0.7169 | 0.1342 | 0.0585 | 0.7049 | 0.9528 | 0.9082 | 0.1536 | 0.0148 |
|  | | 260 | 260 | 260 | 260 | 260 | 260 | 260 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 260 | 260 | 260 | 252 | 260 | 260 | 260 | 260 |
| **Stages** | | -0.03588 | 0.02516 | 1.00000 | 0.24762 | 0.29515 | 0.07754 | -0.19782 | 0.15439 | 0.17218 | 0.10841 | 0.04959 | -0.05577 | 0.03659 | 0.04132 | 0.06777 | 0.05225 | -0.08239 | 0.24240 | 0.17113 | -0.80356 | -0.73948 | -0.07191 | 0.12001 | -0.16070 | -0.33994 | -0.01621 | -0.10153 |
|  | | 0.5639 | 0.6863 |  | <.0001 | <.0001 | 0.2118 | 0.0013 | 0.0143 | 0.0063 | 0.0872 | 0.4341 | 0.3968 | 0.5902 | 0.5497 | 0.3284 | 0.4427 | 0.2988 | 0.0005 | 0.0310 | <.0001 | <.0001 | 0.2470 | 0.0571 | 0.0093 | <.0001 | 0.7944 | 0.1017 |
|  | | 261 | 260 | 261 | 261 | 261 | 261 | 261 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 261 | 261 | 261 | 252 | 261 | 261 | 261 | 261 |
| **Number of metastatic sites** | | 0.06591 | -0.03471 | 0.24762 | 1.00000 | 0.37313 | 0.46296 | -0.17898 | 0.27300 | 0.17469 | 0.18116 | 0.36348 | -0.11440 | 0.14387 | 0.07156 | 0.16089 | 0.17374 | -0.33650 | 0.25458 | 0.21530 | -0.12688 | -0.13402 | -0.04900 | 0.13538 | -0.10673 | -0.34738 | 0.36902 | -0.02636 |
| 0.2888 | 0.5775 | <.0001 |  | <.0001 | <.0001 | 0.0037 | <.0001 | 0.0056 | 0.0041 | <.0001 | 0.0814 | 0.0333 | 0.2997 | 0.0197 | 0.0102 | <.0001 | 0.0002 | 0.0064 | 0.0405 | 0.0304 | 0.4305 | 0.0317 | 0.0853 | <.0001 | <.0001 | 0.6716 |
|  | | 261 | 260 | 261 | 261 | 261 | 261 | 261 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 261 | 261 | 261 | 252 | 261 | 261 | 261 | 261 |
| **Liver metastases** | | -0.07821 | 0.02290 | 0.29515 | 0.37313 | 1.00000 | -0.10922 | -0.27686 | 0.08952 | 0.05559 | 0.18649 | -0.00580 | 0.00159 | 0.11447 | -0.00603 | 0.09283 | 0.17078 | -0.22881 | 0.30165 | 0.24553 | -0.10539 | -0.12126 | -0.06408 | 0.22761 | -0.20317 | -0.31009 | 0.33558 | -0.02170 |
|  | | 0.2079 | 0.7133 | <.0001 | <.0001 |  | 0.0782 | <.0001 | 0.1573 | 0.3815 | 0.0031 | 0.9272 | 0.9807 | 0.0911 | 0.9304 | 0.1802 | 0.0116 | 0.0035 | <.0001 | 0.0018 | 0.0893 | 0.0504 | 0.3024 | 0.0003 | 0.0010 | <.0001 | <.0001 | 0.7271 |
|  | | 261 | 260 | 261 | 261 | 261 | 261 | 261 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 261 | 261 | 261 | 252 | 261 | 261 | 261 | 261 |
| **Peritoneal metastases** | | -0.05167 | -0.01591 | 0.07754 | 0.46296 | -0.10922 | 1.00000 | -0.17898 | 0.25926 | 0.14188 | 0.14304 | 0.47117 | -0.22900 | 0.06508 | 0.08699 | 0.09489 | 0.09335 | -0.20211 | 0.02311 | -0.00808 | -0.04210 | -0.02556 | 0.03491 | -0.00981 | -0.00337 | -0.16829 | 0.27864 | -0.02636 |
| 0.4058 | 0.7985 | 0.2118 | <.0001 | 0.0782 |  | 0.0037 | <.0001 | 0.0249 | 0.0237 | <.0001 | 0.0004 | 0.3377 | 0.2071 | 0.1707 | 0.1696 | 0.0101 | 0.7428 | 0.9195 | 0.4983 | 0.6811 | 0.5745 | 0.8769 | 0.9568 | 0.0064 | <.0001 | 0.6716 |
|  | | 261 | 260 | 261 | 261 | 261 | 261 | 261 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 261 | 261 | 261 | 252 | 261 | 261 | 261 | 261 |
| **Isolated lung metastases** | | 0.10688 | 0.01830 | -0.20557 | -0.31771 | -0.49146 | -0.31771 | 1.00000 | -0.15218 | 0.06536 | -0.09916 | -0.11511 | 0.06888 | -0.00402 | -0.07871 | -0.04621 | -0.06789 | 0.21271 | -0.11784 | -0.06138 | 0.18402 | 0.18800 | 0.01123 | -0.00881 | 0.04804 | 0.02556 | 0.05391 | 0.07840 |
| 0.0848 | 0.7690 | 0.0008 | <.0001 | <.0001 | <.0001 |  | 0.0158 | 0.3033 | 0.1179 | 0.0687 | 0.2951 | 0.9528 | 0.2539 | 0.5054 | 0.3184 | 0.0067 | 0.0932 | 0.4421 | 0.0028 | 0.0023 | 0.8567 | 0.8893 | 0.4397 | 0.3857 | 0.3857 | 0.2068 |
|  | | 261 | 260 | 261 | 261 | 261 | 261 | 261 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 261 | 261 | 261 | 252 | 261 | 261 | 261 | 261 |
| **Performance status (WHO)** | | 0.14152 | 0.14604 | 0.15439 | 0.27300 | 0.08952 | 0.25926 | -0.05374 | 1.00000 | 0.35032 | 0.30444 | 0.31981 | -0.18532 | 0.28287 | 0.11285 | 0.26882 | 0.23101 | -0.35717 | 0.30079 | 0.23139 | -0.16280 | -0.19413 | -0.05361 | 0.04283 | -0.11750 | -0.20878 | 0.13559 | -0.02423 |
| 0.0249 | 0.0206 | 0.0143 | <.0001 | 0.1573 | <.0001 | 0.3965 |  | <.0001 | <.0001 | <.0001 | 0.0045 | <.0001 | 0.1013 | <.0001 | 0.0006 | <.0001 | <.0001 | 0.0033 | 0.0098 | 0.0020 | 0.3977 | 0.5038 | 0.0631 | 0.0009 | 0.0318 | 0.7025 |
|  | | 251 | 251 | 251 | 251 | 251 | 251 | 251 | 251 | 249 | 249 | 250 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 251 | 251 | 251 | 246 | 251 | 251 | 251 | 251 |
| **Pain** | | -0.06185 | 0.08743 | 0.17218 | 0.17469 | 0.05559 | 0.14188 | 0.00430 | 0.35032 | 1.00000 | 0.16009 | 0.26882 | -0.09799 | 0.18040 | 0.05594 | 0.15138 | 0.13250 | -0.20478 | 0.09515 | 0.20281 | -0.20466 | -0.18369 | -0.04924 | -0.09219 | -0.03607 | -0.17825 | -0.03931 | -0.04366 |
|  | | 0.3301 | 0.1682 | 0.0063 | 0.0056 | 0.3815 | 0.0249 | 0.9461 | <.0001 |  | 0.0114 | <.0001 | 0.1367 | 0.0074 | 0.4177 | 0.0283 | 0.0507 | 0.0094 | 0.1769 | 0.0104 | 0.0011 | 0.0036 | 0.4382 | 0.1502 | 0.5702 | 0.0047 | 0.5361 | 0.4920 |
|  | | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 249 | 250 | 249 | 250 | 232 | 219 | 212 | 210 | 218 | 160 | 203 | 159 | 250 | 250 | 250 | 245 | 250 | 250 | 250 | 250 |
| **Jaundice** | | -0.04516 | -0.02154 | 0.10841 | 0.18116 | 0.18649 | 0.14304 | -0.10297 | 0.30444 | 0.16009 | 1.00000 | 0.21792 | -0.03525 | 0.23757 | -0.04586 | 0.15755 | 0.73813 | -0.25911 | 0.24689 | 0.33329 | -0.07547 | -0.07315 | 0.02998 | -0.05060 | 0.00727 | -0.08779 | 0.15659 | 0.02879 |
|  | | 0.4772 | 0.7347 | 0.0872 | 0.0041 | 0.0031 | 0.0237 | 0.1043 | <.0001 | 0.0114 |  | 0.0005 | 0.5932 | 0.0004 | 0.5076 | 0.0227 | <.0001 | 0.0009 | 0.0004 | <.0001 | 0.2344 | 0.2492 | 0.6371 | 0.4304 | 0.9089 | 0.1664 | 0.0132 | 0.6506 |
|  | | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 249 | 249 | 250 | 250 | 232 | 218 | 211 | 209 | 217 | 160 | 202 | 159 | 250 | 250 | 250 | 245 | 250 | 250 | 250 | 250 |
| **Ascites** | | -0.09459 | -0.00770 | 0.04959 | 0.36348 | -0.00580 | 0.47117 | -0.04809 | 0.31981 | 0.26882 | 0.21792 | 1.00000 | -0.18209 | 0.19286 | 0.09467 | 0.20056 | 0.14932 | -0.22694 | 0.08586 | 0.10130 | -0.03489 | -0.08465 | 0.02136 | -0.06377 | 0.00781 | -0.16244 | 0.10709 | 0.03316 |
|  | | 0.1351 | 0.9034 | 0.4341 | <.0001 | 0.9272 | <.0001 | 0.4481 | <.0001 | <.0001 | 0.0005 |  | 0.0053 | 0.0042 | 0.1696 | 0.0035 | 0.0275 | 0.0038 | 0.2232 | 0.2039 | 0.5822 | 0.1813 | 0.7363 | 0.3192 | 0.9020 | 0.0099 | 0.0904 | 0.6010 |
|  | | 251 | 251 | 251 | 251 | 251 | 251 | 251 | 250 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 203 | 159 | 251 | 251 | 251 | 246 | 251 | 251 | 251 | 251 |
| **Hemoglobin** | | -0.02676 | 0.10802 | -0.05577 | -0.11440 | 0.00159 | -0.22900 | 0.10721 | -0.18532 | -0.09799 | -0.03525 | -0.18209 | 1.00000 | -0.03823 | -0.28315 | -0.19177 | -0.00360 | 0.28838 | -0.08633 | -0.14362 | 0.09979 | 0.12089 | 0.04439 | -0.10828 | 0.12910 | 0.18888 | -0.07288 | 0.14689 |
|  | | 0.6845 | 0.1000 | 0.3968 | 0.0814 | 0.9807 | 0.0004 | 0.1026 | 0.0045 | 0.1367 | 0.5932 | 0.0053 |  | 0.5737 | <.0001 | 0.0053 | 0.9583 | 0.0002 | 0.2289 | 0.0746 | 0.1288 | 0.0655 | 0.5002 | 0.1022 | 0.0490 | 0.0038 | 0.2679 | 0.0249 |
|  | | 233 | 233 | 233 | 233 | 233 | 233 | 233 | 233 | 232 | 232 | 233 | 233 | 219 | 211 | 210 | 214 | 159 | 196 | 155 | 233 | 233 | 233 | 229 | 233 | 233 | 233 | 233 |
| **Neutrophils** | | 0.01379 | 0.06128 | 0.03659 | 0.14387 | 0.11447 | 0.06508 | -0.03489 | 0.28287 | 0.18040 | 0.23757 | 0.19286 | -0.03823 | 1.00000 | -0.07298 | 0.74698 | 0.21977 | -0.16769 | 0.26700 | 0.18739 | -0.04071 | -0.02762 | -0.07173 | 0.11008 | -0.15784 | -0.06500 | 0.07184 | 0.10766 |
|  | | 0.8392 | 0.3668 | 0.5902 | 0.0333 | 0.0911 | 0.3377 | 0.6076 | <.0001 | 0.0074 | 0.0004 | 0.0042 | 0.5737 |  | 0.2925 | <.0001 | 0.0014 | 0.0396 | 0.0002 | 0.0204 | 0.5490 | 0.6844 | 0.2906 | 0.1075 | 0.0194 | 0.3383 | 0.2899 | 0.1121 |
|  | | 219 | 219 | 219 | 219 | 219 | 219 | 219 | 219 | 219 | 218 | 219 | 219 | 219 | 210 | 210 | 209 | 151 | 185 | 153 | 219 | 219 | 219 | 215 | 219 | 219 | 219 | 219 |
| **Lymphocytes** | | 0.01932 | -0.04696 | 0.04132 | 0.07156 | -0.00603 | 0.08699 | 0.05528 | 0.11285 | 0.05594 | -0.04586 | 0.09467 | -0.28315 | -0.07298 | 1.00000 | 0.55739 | -0.06244 | -0.11948 | -0.02331 | -0.09540 | -0.11815 | -0.11348 | -0.01582 | -0.08669 | 0.04325 | -0.03626 | -0.03737 | -0.05400 |
|  | | 0.7797 | 0.4964 | 0.5497 | 0.2997 | 0.9304 | 0.2071 | 0.4233 | 0.1013 | 0.4177 | 0.5076 | 0.1696 | <.0001 | 0.2925 |  | <.0001 | 0.3750 | 0.1439 | 0.7561 | 0.2472 | 0.0861 | 0.0994 | 0.8188 | 0.2131 | 0.5312 | 0.5996 | 0.5885 | 0.4341 |
|  | | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 211 | 212 | 211 | 210 | 212 | 210 | 204 | 151 | 180 | 149 | 212 | 212 | 212 | 208 | 212 | 212 | 212 | 212 |
| **Neutrophil-to-lymphocyte ratio** | | -0.00723 | 0.02644 | 0.06777 | 0.16089 | 0.09283 | 0.09489 | 0.00824 | 0.26882 | 0.15138 | 0.15755 | 0.20056 | -0.19177 | 0.74698 | 0.55739 | 1.00000 | 0.11936 | -0.16140 | 0.14222 | 0.06026 | -0.13294 | -0.13314 | -0.04580 | 0.02680 | -0.07283 | -0.08348 | 0.05452 | 0.05677 |
| 0.9171 | 0.7032 | 0.3284 | 0.0197 | 0.1802 | 0.1707 | 0.9056 | <.0001 | 0.0283 | 0.0227 | 0.0035 | 0.0053 | <.0001 | <.0001 |  | 0.0891 | 0.0485 | 0.0576 | 0.4669 | 0.0544 | 0.0540 | 0.5092 | 0.7022 | 0.2935 | 0.2283 | 0.4319 | 0.4132 |
|  | | 210 | 210 | 210 | 210 | 210 | 210 | 210 | 210 | 210 | 209 | 210 | 210 | 210 | 210 | 210 | 204 | 150 | 179 | 148 | 210 | 210 | 210 | 206 | 210 | 210 | 210 | 210 |
| **Total bilirubin** | | -0.05639 | -0.01864 | 0.05225 | 0.17374 | 0.17078 | 0.09335 | -0.06638 | 0.23101 | 0.13250 | 0.73813 | 0.14932 | -0.00360 | 0.21977 | -0.06244 | 0.11936 | 1.00000 | -0.33824 | 0.23961 | 0.27920 | -0.03298 | -0.01054 | 0.02329 | -0.05626 | -0.00158 | -0.02788 | 0.11891 | 0.10890 |
|  | | 0.4074 | 0.7844 | 0.4427 | 0.0102 | 0.0116 | 0.1696 | 0.3293 | 0.0006 | 0.0507 | <.0001 | 0.0275 | 0.9583 | 0.0014 | 0.3750 | 0.0891 |  | <.0001 | 0.0010 | 0.0005 | 0.6282 | 0.8770 | 0.7323 | 0.4129 | 0.9815 | 0.6823 | 0.0798 | 0.1089 |
|  | | 218 | 218 | 218 | 218 | 218 | 218 | 218 | 218 | 218 | 217 | 218 | 214 | 209 | 204 | 204 | 218 | 152 | 185 | 150 | 218 | 218 | 218 | 214 | 218 | 218 | 218 | 218 |
| **Albumin** | | -0.05000 | 0.02184 | -0.08239 | -0.33650 | -0.22881 | -0.20211 | 0.14293 | -0.35717 | -0.20478 | -0.25911 | -0.22694 | 0.28838 | -0.16769 | -0.11948 | -0.16140 | -0.33824 | 1.00000 | -0.19866 | -0.29232 | 0.07057 | 0.05223 | 0.04158 | -0.11311 | 0.16458 | 0.20764 | -0.15539 | -0.12586 |
|  | | 0.5288 | 0.7833 | 0.2988 | <.0001 | 0.0035 | 0.0101 | 0.0705 | <.0001 | 0.0094 | 0.0009 | 0.0038 | 0.0002 | 0.0396 | 0.1439 | 0.0485 | <.0001 |  | 0.0195 | 0.0018 | 0.3737 | 0.5106 | 0.6005 | 0.1570 | 0.0370 | 0.0082 | 0.0490 | 0.1116 |
|  | | 161 | 161 | 161 | 161 | 161 | 161 | 161 | 161 | 160 | 160 | 161 | 159 | 151 | 151 | 150 | 152 | 161 | 138 | 112 | 161 | 161 | 161 | 158 | 161 | 161 | 161 | 161 |
| **CA19-9** | | -0.01179 | 0.11684 | 0.24240 | 0.25458 | 0.30165 | 0.02311 | -0.17131 | 0.30079 | 0.09515 | 0.24689 | 0.08586 | -0.08633 | 0.26700 | -0.02331 | 0.14222 | 0.23961 | -0.19866 | 1.00000 | 0.48837 | -0.19886 | -0.21588 | -0.15866 | 0.23427 | -0.28277 | -0.21302 | 0.14171 | -0.02633 |
| 0.8671 | 0.0961 | 0.0005 | 0.0002 | <.0001 | 0.7428 | 0.0143 | <.0001 | 0.1769 | 0.0004 | 0.2232 | 0.2289 | 0.0002 | 0.7561 | 0.0576 | 0.0010 | 0.0195 |  | <.0001 | 0.0044 | 0.0019 | 0.0234 | 0.0008 | <.0001 | 0.0022 | 0.0432 | 0.7085 |
|  | | 204 | 204 | 204 | 204 | 204 | 204 | 204 | 204 | 203 | 202 | 203 | 196 | 185 | 180 | 179 | 185 | 138 | 204 | 155 | 204 | 204 | 204 | 202 | 204 | 204 | 204 | 204 |
| **CEA** | | 0.04026 | 0.04883 | 0.17113 | 0.21530 | 0.24553 | -0.00808 | -0.09340 | 0.23139 | 0.20281 | 0.33329 | 0.10130 | -0.14362 | 0.18739 | -0.09540 | 0.06026 | 0.27920 | -0.29232 | 0.48837 | 1.00000 | -0.16833 | -0.17579 | -0.10403 | 0.08657 | -0.12113 | -0.17255 | 0.13125 | -0.09269 |
| 0.6143 | 0.5411 | 0.0310 | 0.0064 | 0.0018 | 0.9195 | 0.2416 | 0.0033 | 0.0104 | <.0001 | 0.2039 | 0.0746 | 0.0204 | 0.2472 | 0.4669 | 0.0005 | 0.0018 | <.0001 |  | 0.0339 | 0.0267 | 0.1919 | 0.2810 | 0.1283 | 0.0296 | 0.0991 | 0.2452 |
|  | | 159 | 159 | 159 | 159 | 159 | 159 | 159 | 159 | 159 | 159 | 159 | 155 | 153 | 149 | 148 | 150 | 112 | 155 | 159 | 159 | 159 | 159 | 157 | 159 | 159 | 159 | 159 |
| **Primary tumor resection** | | 0.07004 | -0.02259 | -0.80356 | -0.12688 | -0.10539 | -0.04210 | -0.06525 | -0.16280 | -0.20466 | -0.07547 | -0.03489 | 0.09979 | -0.04071 | -0.11815 | -0.13294 | -0.03298 | 0.07057 | -0.19886 | -0.16833 | 1.00000 | 0.86061 | 0.12834 | -0.15156 | 0.21652 | 0.38914 | 0.11878 | 0.10208 |
| 0.2596 | 0.7169 | <.0001 | 0.0405 | 0.0893 | 0.4983 | 0.2936 | 0.0098 | 0.0011 | 0.2344 | 0.5822 | 0.1288 | 0.5490 | 0.0861 | 0.0544 | 0.6282 | 0.3737 | 0.0044 | 0.0339 |  | <.0001 | 0.0383 | 0.0160 | 0.0004 | <.0001 | 0.0553 | 0.0998 |
|  | | 261 | 260 | 261 | 261 | 261 | 261 | 261 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 261 | 261 | 261 | 252 | 261 | 261 | 261 | 261 |
| **Adjuvant chemotherapy** | | 0.02835 | -0.09312 | -0.73948 | -0.13402 | -0.12126 | -0.02556 | -0.06282 | -0.19413 | -0.18369 | -0.07315 | -0.08465 | 0.12089 | -0.02762 | -0.11348 | -0.13314 | -0.01054 | 0.05223 | -0.21588 | -0.17579 | 0.86061 | 1.00000 | 0.04846 | -0.10549 | 0.14050 | 0.38008 | 0.10440 | 0.11957 |
| 0.6485 | 0.1342 | <.0001 | 0.0304 | 0.0504 | 0.6811 | 0.3120 | 0.0020 | 0.0036 | 0.2492 | 0.1813 | 0.0655 | 0.6844 | 0.0994 | 0.0540 | 0.8770 | 0.5106 | 0.0019 | 0.0267 | <.0001 |  | 0.4357 | 0.0947 | 0.0232 | <.0001 | 0.0923 | 0.0537 |
|  |  | 261 | 260 | 261 | 261 | 261 | 261 | 261 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 261 | 261 | 261 | 252 | 261 | 261 | 261 | 261 |
| **First-line chemo therapy** | **Number of cures** | 0.08083 | -0.11749 | -0.07191 | -0.04900 | -0.06408 | 0.03491 | -0.08473 | -0.05361 | -0.04924 | 0.02998 | 0.02136 | 0.04439 | -0.07173 | -0.01582 | -0.04580 | 0.02329 | 0.04158 | -0.15866 | -0.10403 | 0.12834 | 0.04846 | 1.00000 | -0.41322 | 0.69973 | -0.00502 | 0.08421 | 0.15058 |
| 0.1930 | 0.0585 | 0.2470 | 0.4305 | 0.3024 | 0.5745 | 0.1723 | 0.3977 | 0.4382 | 0.6371 | 0.7363 | 0.5002 | 0.2906 | 0.8188 | 0.5092 | 0.7323 | 0.6005 | 0.0234 | 0.1919 | 0.0383 | 0.4357 |  | <.0001 | <.0001 | 0.9357 | 0.1750 | 0.0149 |
|  | 261 | 260 | 261 | 261 | 261 | 261 | 261 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 261 | 261 | 261 | 252 | 261 | 261 | 261 | 261 |
| **RECIST Best response** | 0.06080 | -0.02397 | 0.12001 | 0.13538 | 0.22761 | -0.00981 | -0.17511 | 0.04283 | -0.09219 | -0.05060 | -0.06377 | -0.10828 | 0.11008 | -0.08669 | 0.02680 | -0.05626 | -0.11311 | 0.23427 | 0.08657 | -0.15156 | -0.10549 | -0.41322 | 1.00000 | -0.69690 | -0.42675 | 0.25902 | -0.05724 |
| 0.3364 | 0.7049 | 0.0571 | 0.0317 | 0.0003 | 0.8769 | 0.0053 | 0.5038 | 0.1502 | 0.4304 | 0.3192 | 0.1022 | 0.1075 | 0.2131 | 0.7022 | 0.4129 | 0.1570 | 0.0008 | 0.2810 | 0.0160 | 0.0947 | <.0001 |  | <.0001 | <.0001 | <.0001 | 0.3656 |
|  | 252 | 252 | 252 | 252 | 252 | 252 | 252 | 246 | 245 | 245 | 246 | 229 | 215 | 208 | 206 | 214 | 158 | 202 | 157 | 252 | 252 | 252 | 252 | 252 | 252 | 252 | 252 |
| **Duration of L1** | -0.02969 | -0.00369 | -0.16070 | -0.10673 | -0.20317 | -0.00337 | 0.11191 | -0.11750 | -0.03607 | 0.00727 | 0.00781 | 0.12910 | -0.15784 | 0.04325 | -0.07283 | -0.00158 | 0.16458 | -0.28277 | -0.12113 | 0.21652 | 0.14050 | 0.69973 | -0.69690 | 1.00000 | 0.35712 | -0.06440 | -0.06523 |
| 0.6330 | 0.9528 | 0.0093 | 0.0853 | 0.0010 | 0.9568 | 0.0711 | 0.0631 | 0.5702 | 0.9089 | 0.9020 | 0.0490 | 0.0194 | 0.5312 | 0.2935 | 0.9815 | 0.0370 | <.0001 | 0.1283 | 0.0004 | 0.0232 | <.0001 | <.0001 |  | <.0001 | 0.3000 | 0.2938 |
| 261 | 260 | 261 | 261 | 261 | 261 | 261 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 261 | 261 | 261 | 252 | 261 | 261 | 261 | 261 |
| **Reason for discontinuation** | -0.04457 | 0.00719 | -0.33994 | -0.34738 | -0.31009 | -0.16829 | 0.32421 | -0.20878 | -0.17825 | -0.08779 | -0.16244 | 0.18888 | -0.06500 | -0.03626 | -0.08348 | -0.02788 | 0.20764 | -0.21302 | -0.17255 | 0.38914 | 0.38008 | -0.00502 | -0.42675 | 0.35712 | 1.00000 | -0.43976 | -0.05415 |
| 0.4734 | 0.9082 | <.0001 | <.0001 | <.0001 | 0.0064 | <.0001 | 0.0009 | 0.0047 | 0.1664 | 0.0099 | 0.0038 | 0.3383 | 0.5996 | 0.2283 | 0.6823 | 0.0082 | 0.0022 | 0.0296 | <.0001 | <.0001 | 0.9357 | <.0001 | <.0001 |  | <.0001 | 0.3836 |
|  | 261 | 260 | 261 | 261 | 261 | 261 | 261 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 261 | 261 | 261 | 252 | 261 | 261 | 261 | 261 |
| **Metastatic progression** | -0.03999 | 0.08874 | -0.01621 | 0.36902 | 0.33558 | 0.27864 | -0.61614 | 0.13559 | -0.03931 | 0.15659 | 0.10709 | -0.07288 | 0.07184 | -0.03737 | 0.05452 | 0.11891 | -0.15539 | 0.14171 | 0.13125 | 0.11878 | 0.10440 | 0.08421 | 0.25902 | -0.06440 | -0.43976 | 1.00000 | 0.11396 |
| 0.5201 | 0.1536 | 0.7944 | <.0001 | <.0001 | <.0001 | <.0001 | 0.0318 | 0.5361 | 0.0132 | 0.0904 | 0.2679 | 0.2899 | 0.5885 | 0.4319 | 0.0798 | 0.0490 | 0.0432 | 0.0991 | 0.0553 | 0.0923 | 0.1750 | <.0001 | 0.3000 | <.0001 |  | 0.0660 |
|  | 261 | 260 | 261 | 261 | 261 | 261 | 261 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 261 | 261 | 261 | 252 | 261 | 261 | 261 | 261 |
| **Type of L2 regimen** | | 0.16440 | -0.15106 | -0.10153 | -0.02636 | -0.02170 | -0.02636 | -0.10421 | -0.02423 | -0.04366 | 0.02879 | 0.03316 | 0.14689 | 0.10766 | -0.05400 | 0.05677 | 0.10890 | -0.12586 | -0.02633 | -0.09269 | 0.10208 | 0.11957 | 0.15058 | -0.05724 | -0.06523 | -0.05415 | 0.11396 | 1.00000 |
| 0.0078 | 0.0148 | 0.1017 | 0.6716 | 0.7271 | 0.6716 | 0.0930 | 0.7025 | 0.4920 | 0.6506 | 0.6010 | 0.0249 | 0.1121 | 0.4341 | 0.4132 | 0.1089 | 0.1116 | 0.7085 | 0.2452 | 0.0998 | 0.0537 | 0.0149 | 0.3656 | 0.2938 | 0.3836 | 0.0660 |  |
| 261 | 260 | 261 | 261 | 261 | 261 | 261 | 251 | 250 | 250 | 251 | 233 | 219 | 212 | 210 | 218 | 161 | 204 | 159 | 261 | 261 | 261 | 252 | 261 | 261 | 261 | 261 |

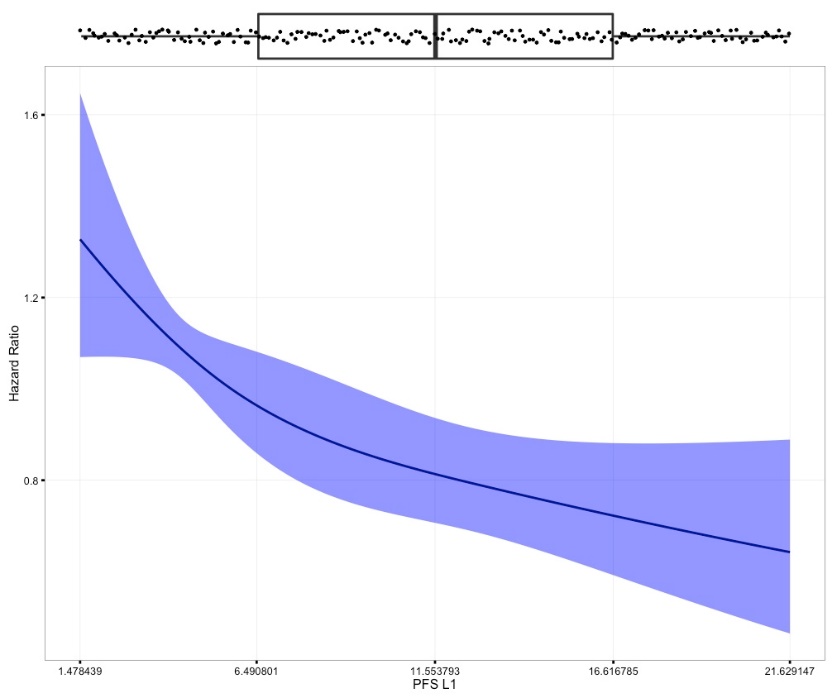
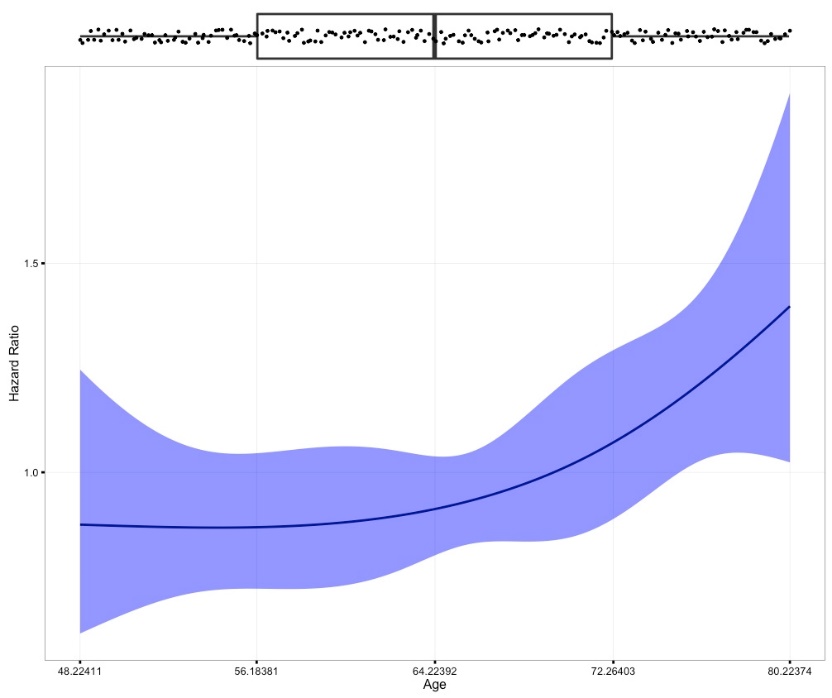
**Supplementary Figure 1. Correlation matrix**

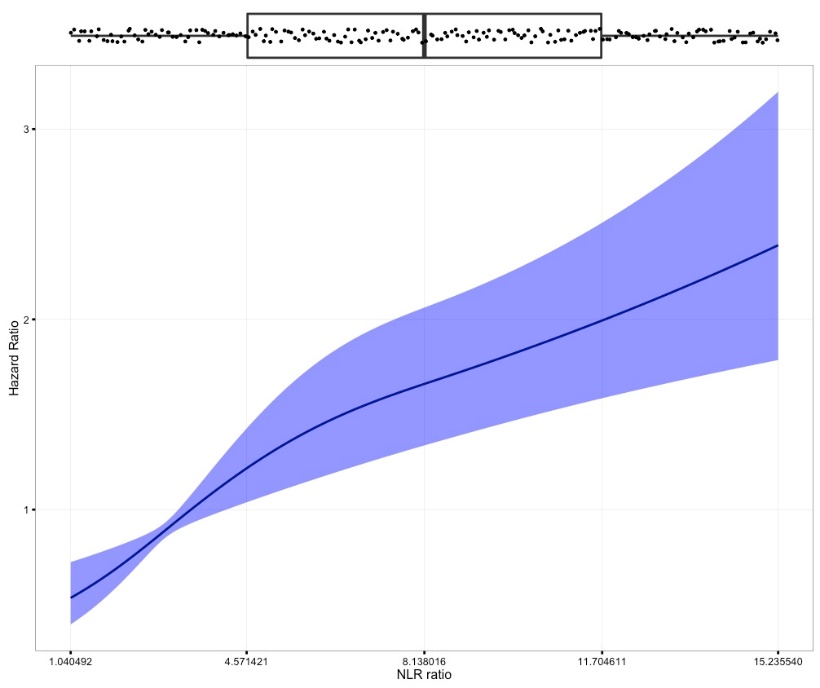
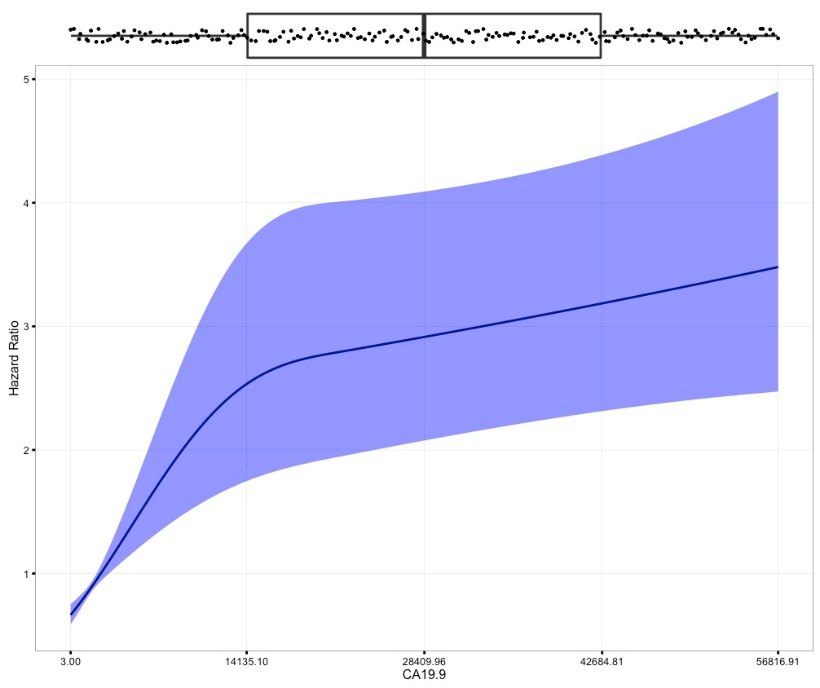
Pearson correlation coefficients: < 0.2 – 0.2-0.3 – 0.3-0.4 – ≥ 0.4 P-value: > 0.001 – ≤ 0.001

The significant correlations were defined by a correlation coefficient ≥ 0.4 associated with a P-value < 0.001:

* among “Tumor stage”, “Primary tumor resection” and “Adjuvant chemotherapy”, the parameter “Tumor stage” is selected
* between “Ascites” and “Peritoneal metastases”, the parameter “Ascites” is selected
* between “Number of metastatic sites” and “Peritoneal metastases”, the parameter “Number of metastatic sites” is selected
* among “Number of cures in first-line chemotherapy”, “RECIST Best response” and “Duration of first-line chemotherapy”, the parameter “Duration of first-line chemotherapy” is selected
* between “Reason for discontinuation in first-line chemotherapy” and “Metastatic progression in first-line chemotherapy”, the parameter “Metastatic progression in first-line chemotherapy” is selected
* between “RECIST Best response in first-line chemotherapy” and “Reason for discontinuation in first-line chemotherapy”, none of these parameters is selected
* between “Total bilirubin” and “Jaundice”, the parameter “Jaundice” is selected
* between “CA19-9” and “CEA”, the parameter “CA19-9” is selected

Abbreviations: WHO=World Health Organization, CA 19-9=Carbohydrate Antigen 19-9, CEA=Carcinoembryonic Antigen, L1=first-line chemotherapy, L2=second-line chemotherapy

**Age Duration of first-line chemotherapy (L1)**

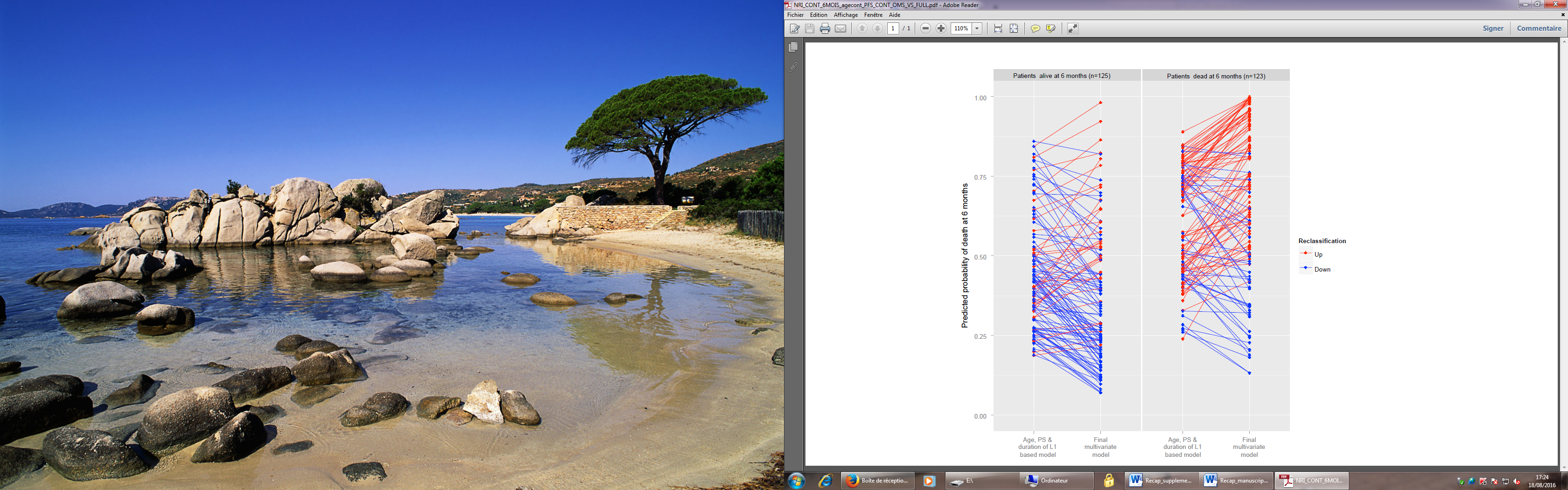
**Neutrophil-to-lymphocyte ratio (NLR) Carbohydrate antigen 19-9 (CA 19-9)**

# **Supplementary Figure 2. Restricted cubic spline modelization.** A square root transformation was applied for neutrophil count, neutrophil-to-lymphocyte ratio (NLR), total bilirubin, and carbohydrate antigen 19-9 (CA 19-9), while a logarithmic transformation was used for platelets count, carcinoembryonic antigen (CEA), and duration of first-line chemotherapy (L1). An inverse transformation was necessary for lymphocyte count. All other continuous variables were considered without any transformation.

Diapositive1Diapositive4Diapositive2

Diapositive3

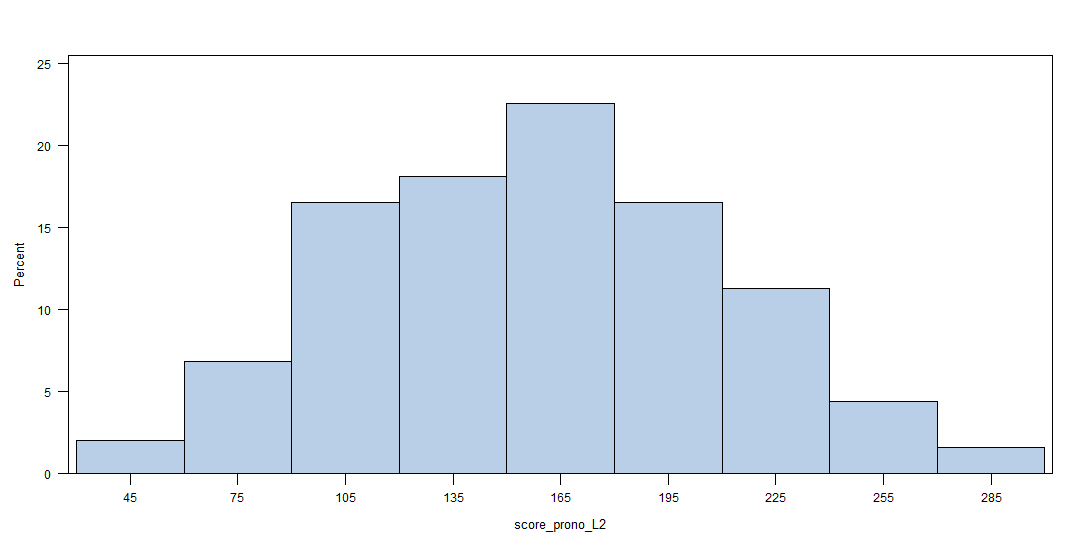
**Supplementary Figure 3. Calibration plots at 6, 12, 18 and 24 months for the final multivariate model.** Vertical axis is the observed proportion of patients surviving at time of interest. Black line=observed; Grey line=ideal calibrated model; Blue line=bootstrap corrected estimates (optimism corrected). B= 20 repetitions for bootstrap.



# **Supplementary Figure 4. Continuous net reclassification improvement (cNRI).** Additive value of the other parameters among the classical approach (“pragmatic parameters”: age, performance status (PS) and duration of first-line chemotherapy (L1)) for the reclassification of death risk at 6 months post-L1 (continuous net reclassification improvement). Blue lines in patients alive at 6 months indicate that the other parameters moved risk prediction in the correct (downward) direction (92/125 = 73.6%). Conversely, red lines in patients died at 6 months indicate a correct (upward) change in risk assessment when using the final multivariate model (81/123 = 65.9%).

Macintosh HD:Users:Dewi:Documents:CHU_besancon:RECAP-angelique_viennot:L2_UNRESECTABLE:IDI_FIG.pdf

# **Supplementary Figure 5. Integrated discrimination improvement (IDI).** Improvement in calculated risk of death at 6 months by considering the 6 other parameters in addition to pragmatic parameters. Improvement in calculated risk of death at 6 months was assessed by the IDI. The IDI integrates the change in mean predicted probability of death 6 months in patients with dead and those alive at 6 months. The change in the mean predicted probability of death is adequate if it is positive for deceased patients (increased calculated risk) and negative for those alive (decreased calculated risk).

**Supplementary Figure 6. Distribution prognostic score.** Mean = 159.7; Standard deviation = 52.5.

Pronostic score value

Diapositive6Diapositive1

A

B

# **Supplementary Figure 7. Kaplan-Meier curves of overall survival for two risk groups in the development cohort (A) and in the external validation cohort (B).** Values of the log-rank test P<0.05 were considered statistically significant and all tests were two-sided. Abbreviation: CI=confidence interval.

Diapositive12

# **Supplementary Figure 8. Kaplan-Meier curves of overall survival three risk groups without second-line chemotherapy administration.** Values of the log-rank test P<0.05 were considered statistically significant and all tests were two-sided**.** Abbreviation: CI=confidence interval.

Diapositive16**Low risk group Intermediate risk group**

Diapositive17

Diapositive18**High risk group**

# **Supplementary Figure 9. Kaplan-Meier curves of overall survival for second-line chemotherapy administration according to the repartition between the three risk groups.** Values of the log-rank test P<0.05 were considered statistically significant and all tests were two-sided**.** Abbreviations: HR=Hazard Ratio, NA= not available, CI=confidence interval, L2=second-line chemotherapy.

Diapositive25

# **Supplementary Figure 10. Kaplan-Meier curves of progression free survival for three risk groups for the development cohort.** Values of the log-rank test P<0.05 were considered statistically significant and all tests were two-sided**.** Abbreviation: CI=confidence interval.

Diapositive23

# **Supplementary Figure 11. Kaplan-Meier curves of progression free survival for two risk groups for the development cohort.** Values of the log-rank test P<0.05 were considered statistically significant and all tests were two-sided. Abbreviation: CI=confidence interval.