**Table S1. Stratifications for randomization of this study**

|  |  |  |
| --- | --- | --- |
| **Primary side and with/without bevacizumab** | **Group** | **No. of patients** |
| Left side and with bevacizumab | Control | 73 |
|  | Experimental | 81 |
| Left side and without bevacizumab | Control | 85 |
|  | Experimental | 80 |
| Right side and with bevacizumab | Control | 32 |
|  | Experimental | 27 |
| Right side and without bevacizumab | Control | 31 |
|  | Experimental | 33 |

Footnotes: Control, Chemotherapy only; Experimental, Chemotherapy plus high-dose vitamin C

**Table S2. Efficacy and best response of patients with RAS mutation in different treatment groups**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Experimental Group(*N* = 103) | Control Group(*N* = 100) | *P* value |
| **Efficacy** |  |  |  |
| ORR | 43 | 42 | 0.8 |
| % (95% CI) | 41.7 (32.2-51.9) | 42.0 (32.3-52.3) |  |
| DCR | 86 | 79 | 0.7 |
| % (95% CI) | 83.5 (74.6-89.8) | 79.0 (69.5-86.2) |  |
| **Best response, n (%)** |  |  | 0.8 |
| PR | 43 (41.7)  | 42 (42.0)  |  |
| SD | 43 (41.7)  | 37 (37.0)  |  |
| PD | 12 (11.7)  | 14 (14.0)  |  |
| NE |  5 (4.9)  |  7 (7.0)  |  |

Abbreviation: ORR: objective response rate; DCR: disease control rate; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated

Footnotes: Control Group, Chemotherapy only; Experimental Group, Chemotherapy plus high-dose vitamin C

**Table S3. Stratification statuses and teatment features of patients with RAS mutation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Experimental Group(*N* = 103) | Control Group(*N* = 100) | *P* value |
| **Primary tumor site** |  |  |  | 0.8 |
|  | Left | 74 (71.8) | 69 (69.0) |  |
|  | Right | 29 (28.2) | 31 (31.0) |  |
| **Bevacizumab prescription** |  |  |  | 1.0 |
|  | No | 47 (45.6) | 45 (45.0) |  |
|  | Yes | 56 (54.4) | 55 (55.0) |  |
| **Maintenance Therapy** |  |  |  | 0.9 |
|  | No | 73 (70.9) | 69 (69.0) |  |
|  | Yes | 30 (29.1) | 31 (31.0) |  |
| **Primary side and with/without bevacizumab** |  |  |  | 0.9 |
|  | Left side and with bevacizumab | 42 (40.8) | 38 (38.0) |  |
|  | Left side and without bevacizumab | 32 (31.1) | 31 (31.0) |  |
|  | Right side and with bevacizumab | 14 (13.6) | 17 (17.0) |  |
|  | Right side and without bevacizumab | 15 (14.6) | 14 (14.0) |  |
| **Treatment cycle (median)** |  | 8.0 | 8.0 |  1.0 |
| **Treatment duration (median)** |  | 4.77 | 4.40 |  0.7 |

Footnotes: Control Group, Chemotherapy only; Experimental Group, Chemotherapy plus high-dose vitamin C

**Table S4. Univariate and multivariate analysis of progression-free survival in patients with RAS mutation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Univariate analysis** |  | **Multivariate analysis** |
|  |  | **HR** | **95%CI** | ***P* value** |  | **HR** | **95%CI** | ***P* value** |
| **Group** |  |  |  |  |  |  |  |  |
|  | Control | Reference |  |  |  |  |  |  |
|  | Experimental | 0.67 | 0.50-0.91 | 0.01\* |  | 0.64 | 0.47-0.87 | 0.004\* |
| **Bevacizumab prescription** |  |  |  |  |  |  |  |  |
|  | No | Reference |  |  |  |  |  |  |
|  | Yes | 0.74 | 0.54-0.995 | 0.047\* |  | 0.69 | 0.51-0.94 | 0.02\* |
| **Primary tumor site** |  |  |  |  |  |  |  |  |
|  | Left | Reference |  |  |  |  |  |  |
|  | Right | 1.3 | 0.93-1.76 | 0.1 |  |  |  |  |
| **Age** |  |  |  |  |  |  |  |  |
|  | ≥55 | Reference |  |  |  |  |  |  |
|  | <55 | 1.1 | 0.83-1.53 | 0.5 |  |  |  |  |

Footnotes: Control Group, Chemotherapy only; Experimental Group, Chemotherapy plus high-dose vitamin C; \**P*-value <0.05

**Table S5. Treatment-related adverse events reported in less than 10% of the patients**

|  |  |  |  |
| --- | --- | --- | --- |
| 　 | All patients (*N* = 442) | Experimental Group(*N* = 221) | Control Group(*N* = 221) |
| Adverse Event | Any | ≥ Grade 3 | Any | ≥ Grade 3 | Any | ≥ Grade 3 |
| Total | 373 (84.4) | 141 (31.9) | 192 (86.9) | 74 (33.5) | 181 (81.9) | 67 (30.3) |
| Abdominal pain | 35 (7.9) | 0 | 21 (9.5) | 0 | 14 (6.3) | 0 |
| Hypertension | 29 (6.6) | 4 (0.9) | 17 (7.7) | 3 (1.4) | 12 (5.4) | 1 (0.5) |
| Hand-foot syndrome | 28 (6.3) | 1 (0.2) | 20 (9.0) | 1 (0.5) | 8 (3.6) | 0 |
| Oral mucositis | 27 (6.1) | 2 (0.5) | 16 (7.2) | 1 (0.5) | 11 (5.0) | 1 (0.5) |
| Intestinal obstruction | 26 (5.9) | 15 (3.4) | 14 (6.3) | 5 (2.3) | 12 (5.4) | 10 (4.5) |
| Hyperlipidemia | 26 (5.9) | 0 | 16 (7.2) | 0 | 10 (4.5) | 0 |
| Hyperglycemia | 24 (5.4) | 1 (0.2) | 12 (5.4) | 1 (0.5) | 12 (5.4) | 0 |
| Jaundice | 21 (4.8) | 1 (0.2) | 13 (5.9) | 1 (0.5) | 8 (3.6) | 0 |
| Lymphocytosis | 20 (4.5) | 2 (0.5) | 13 (5.9) | 1 (0.5) | 7 (3.2) | 1 (0.5) |
| Glutamyltransferase elevation | 20 (4.5) | 2 (0.5) | 13 (5.9) | 2 (0.9) | 7 (3.2) | 0 |
| Insomnia | 17 (3.8) | 0 | 7 (3.2) | 0 | 10 (4.5) | 0 |
| Constipation | 14 (3.2) | 0 | 9 (4.1) | 0 | 5 (2.3) | 0 |
| Pain | 14 (3.2) | 1 (0.2) | 5 (2.3) | 0 | 9 (4.1) | 1 (0.5) |
| Hypokalemia | 12 (2.7) | 2 (0.5) | 3 (1.4) | 1 (0.5) | 9 (4.1) | 1 (0.5) |
| Fever | 11 (2.5) | 1 (0.2) | 7 (3.2) | 1 (0.5) | 4 (1.8) | 0 |
| Hair loss | 11 (2.5) | 0 | 4 (1.8) | 0 | 7 (3.2) | 0 |
| Swelling and aching of the gum | 10 (2.3) | 0 | 5 (2.3) | 0 | 5 (2.3) | 0 |
| Increased creatinine | 10 (2.3) | 1 (0.2) | 4 (1.8) | 1 (0.5) | 6 (2.7) | 0 |
| Abdominal distention | 10 (2.3) | 0 | 5 (2.3) | 0 | 5 (2.3) | 0 |
| Arrhythmia | 9 (2.0) | 0 | 6 (2.7) | 0 | 3 (1.4) | 0 |
| Gastrointestinal bleeding | 9 (2.0) | 0 | 4 (1.8) | 0 | 5 (2.3) | 0 |
| Hyponatremia | 8 (1.8) | 0 | 4 (1.8) | 0 | 4 (1.8) | 0 |
| Cough | 7 (1.6) | 0 | 4 (1.8) | 0 | 3 (1.4) | 0 |
| Dizziness | 7 (1.6) | 0 | 3 (1.4) | 0 | 4 (1.8) | 0 |
| Epistaxis | 7 (1.6) | 1 (0.2) | 4 (1.8) | 0 | 3 (1.4) | 1 (0.5) |
| Allergy (Oxaliplatin) | 6 (1.4) | 3 (0.7) | 2 (0.9) | 1 (0.5) | 4 (1.8) | 2 (0.9) |
| Rash | 6 (1.4) | 0 | 6 (2.7) | 0 | 0 | 0 |
| Hoarseness | 5 (1.1) | 0 | 4 (1.8) | 0 | 1 (0.5) | 0 |
| Chest pain | 5 (1.1) | 0 | 4 (1.8) | 0 | 1 (0.5) | 0 |
| Xerostomia | 4 (0.9) | 0 | 3 (1.4) | 0 | 1 (0.5) | 0 |
| Oral hemorrhage | 4 (0.9) | 0 | 1 (0.5) | 0 | 3 (1.4) | 0 |
| Skin pigmentation | 4 (0.9) | 0 | 3 (1.4) | 0 | 1 (0.5) | 0 |
| Hematuria | 4 (0.9) | 0 | 3 (1.4) | 0 | 1 (0.5) | 0 |
| Weight loss | 3 (0.7) | 0 | 1 (0.5) | 0 | 2 (0.9) | 0 |
| Headache | 3 (0.7) | 0 | 2 (0.9) | 0 | 1 (0.5) | 0 |
| Hiccup | 2 (0.5) | 0 | 2 (0.9) | 0 | 0 | 0 |
| Hemoptysis | 2 (0.5) | 0 | 2 (0.9) | 0 | 0 | 0 |
| Urinary tract infection | 2 (0.5) | 0 | 2 (0.9) | 0 | 0 | 0 |
| Tinnitus | 2 (0.5) | 0 | 2 (0.9) | 0 | 0 | 0 |
| Intestinal perforation | 2 (0.5) | 2 (0.5) | 1 (0.5) | 1 (0.5) | 1 (0.5) | 1 (0.5) |
| Thrombosis | 2 (0.5) | 0 | 0 | 0 | 2 (0.9) | 0 |
| Septicemia | 2 (0.5) | 2 (0.5) | 2 (0.9) | 2 (0.9) | 0 | 0 |
| Stoma bleeding | 2 (0.5) | 0 | 1 (0.5) | 0 | 1 (0.5) | 0 |
| Hyperkalemia | 2 (0.5) | 0 | 1 (0.5) | 0 | 1 (0.5) | 0 |
| Hypocalcemia | 1 (0.2) | 0 | 1 (0.5) | 0 | 0 | 0 |
| Lower limb edema | 1 (0.2) | 0 | 0 | 0 | 1 (0.5) | 0 |
| Intestinal fistula | 1 (0.2) | 0 | 0 | 0 | 1 (0.5) | 0 |
| Pulmonary infection | 1 (0.2) | 1 (0.2) | 0 | 0 | 1 (0.5) | 1 (0.5) |
| Cerebral hemorrhage | 1 (0.2) | 1 (0.2) | 1 (0.5) | 1 (0.5) | 0 | 0 |
| Colporrhagia | 1 (0.2) | 0 | 1 (0.5) | 0 | 0 | 0 |
| Hypernatremia | 1 (0.2) | 0 | 1 (0.5) | 0 | 0 | 0 |

Footnotes: Control Group, Chemotherapy only; Experimental Group, Chemotherapy plus high-dose vitamin C