**Supplementary Information**

**Table S1. Univariable logistic and Cox regression analyses for RR, PFS, and OS.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **RR** |  | **PFS** |  | **OS** |  |
|  | **OR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| **Race** |  | ***0.004*** |  | ***0.004*** |  | ***<0.001*** |
| **Caucasian** | Reference |  | Reference |  | Reference |  |
| **Others\*** | 9.857 (2.273,54.832) |  | 3.362 (1.546,7.312) |  | 8.666 (2.871,26.159) |  |
| **Smoking Status** |  | 0.208 |  | 0.221 |  | 0.608 |
| **No** | Reference |  | Reference |  | Reference |  |
| **Yes** | 2.273 (0.647,8.540) |  | 1.51 (0.78,2.926) |  | 1.305 (0.471,3.610) |  |
| **Number of Prior anti-VEGF Therapies** |  | 0.165 |  | 0.167 |  | ***0.021*** |
| **≤ 1** | Reference |  | Reference |  | Reference |  |
| **> 1** | 2.593 (0.680,10.357) |  | 1.668 (0.825,3.374) |  | 3.424 (1.226,9.566) |  |
| **Number of Prior anti-VEGF Therapies (Continuous)** | 1.412 (0.898,2.333) | 0.146 | 1.135 (0-.901,1.430) | 0.282 | 1.429 (1.018,2.006) | ***0.039*** |
| **NLR at Day 15** |  | 0.150 |  | ***0.009*** |  | ***0.008*** |
| **< 3** | Reference |  | Reference |  | Reference |  |
| **≥ 3** | 2.750 (0.728,12.047) |  | 2.532 (1.241,5.166) |  | 4.856 (1.309,18.011) |  |
| **NLR at Cycle 3** |  | 0.286 |  | ***0.004*** |  | ***0.001*** |
| **< 3** | Reference |  | Reference |  | Reference |  |
| **≥ 3** | 2.333 (0.521,12.728) |  | 3.017 (1.386,6.569) |  | 12.935 (1.641,101.941) |  |
| **MSKCC Prognostic Score** |  | 0.473 |  | 0.462 |  | 0.111 |
| **Low** | Reference |  | Reference |  | Reference |  |
| **Intermediate** | 0.614 (0.159,2.372) |  | 0.764 (0.378,1.548) |  | 0.428 (0.154,1.187) |  |

\*, Others include African-American and Asian.

**Table S2. Univariable and multivariable logistic and Cox regression analyses of risk factors associated with RR, PFS, and OS. Note ‘Pretherapy NLR’ is grouped by its median of 3.2.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **RR\*** | | | | **PFS#** | | | | **OS$** | | | |
|  | **Univariable analysis** | | **Multivariable analysis** | | **Univariable analysis** | | **Multivariable analysis** | | **Univariable analysis** | | **Multivariable analysis** | |
|  | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| **Heng Prognostic Score** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Low** | Reference |  | Reference |  | Reference |  | Reference |  | Reference |  | Reference |  |
| **Int/High^** | 0.500 (0.124,1.973) | 0.319 | 0.551 (0.130,2.303) | 0.409 | 0.779 (0.379,1.6) | 0.496 | 0.911 (0.442,1.876) | 0.799 | 0.514 (0.182,1.451) | 0.201 | 0.591 (0.209,1.671) | 0.321 |
| **Duration of prior anti-VEGF Therapies** |  |  |  |  |  |  |  |  |  |  |  |  |
| **<6 Months** | Reference |  | Reference |  | Reference |  | Reference |  | Reference |  | Reference |  |
| **≥6 Months** | 2.200 (0.613,8.678) | 0.237 | 2.363 (0.636,9.841) | 0.212 | 2.015 (1.046,3.883) | ***0.048*** | 2.298 (1.102,4.792) | ***0.027*** | 2.869 (0.9,9.141) | 0.063 | 2.978 (0.929,9.55) | 0.066 |
| **Pretherapy NLR** |  |  |  |  |  |  |  |  |  |  |  |  |
| **<3.2** | Reference |  | Reference |  | Reference |  | Reference |  | Reference |  | Reference |  |
| **≥3.2** | 1.944 (0.554,7.257) | 0.306 | 1.926 (0.516,7.653) | 0.335 | 2.466 (1.253,4.853) | ***0.009*** | 2.731 (1.358,5.491) | ***0.005*** | 3.121 (1.039,9.37) | ***0.042*** | 3.156 (1.02,9.763) | ***0.046*** |

^, Intermediate and high; \*, PD1/PDL1 response rate to progression disease and non-response; #, progression-free survival; $, overall survival.

**Table S3. Univariable and multivariable logistic and Cox regression analyses of risk factors associated with RR, PFS, and OS. Note ‘Pretherapy NLR’ is considered as a continuous variable.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **RR\*** | | | | **PFS#** | | | | **OS$** | | | |
|  | **Univariable analysis** | | **Multivariable analysis** | | **Univariable analysis** | | **Multivariable analysis** | | **Univariable analysis** | | **Multivariable analysis** | |
|  | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| **Heng Prognostic Score** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Low** | Reference |  | Reference |  | Reference |  | Reference |  | Reference |  | Reference |  |
| **Int/High^** | 0.500 (0.124,1.973) | 0.319 | 0.468 (0.110,1.919) | 0.290 | 0.779 (0.379,1.6) | 0.496 | 0.656 (0.308,1.398) | 0.274 | 0.514 (0.182,1.451) | 0.201 | 0.533 (0.187,1.513) | 0.237 |
| **Duration of prior anti-VEGF Therapies** |  |  |  |  |  |  |  |  |  |  |  |  |
| **<6 Months** | Reference |  | Reference |  | Reference |  | Reference |  | Reference |  | Reference |  |
| **≥6 Months** | 2.200 (0.613,8.678) | 0.237 | 2.206 (0.600,8.947) | 0.244 | 2.015 (1.046,3.883) | ***0.048*** | 1.885 (0.908,3.913) | 0.089 | 2.869 (0.9,9.141) | 0.063 | 2.541 (0.781,8.271) | 0.122 |
| **Pretherapy NLR** | 1.102 (0.848,1.449) | 1.449 | 1.115 (0.851,1.479) | 0.423 | 1.328 (1.146,1.538) | ***<0.001*** | 1.337 (1.149,1.556) | ***<0.001*** | 1.123 (0.926,1.361) | 0.237 | 1.091 (0.901,1.321) | 0.371 |

^, Intermediate and high; \*, PD1/PDL1 response rate to progression disease and non-response; #, progression-free survival; $, overall survival.

**Table S4. Univariable and multivariable Cox regression analyses of risk factors associated with PFS. Note that two variables ‘Duration of prior anti-VEGF Therapies’ and ‘Pretherapy NLR (with the cutoff value of 3)’ are combined.**

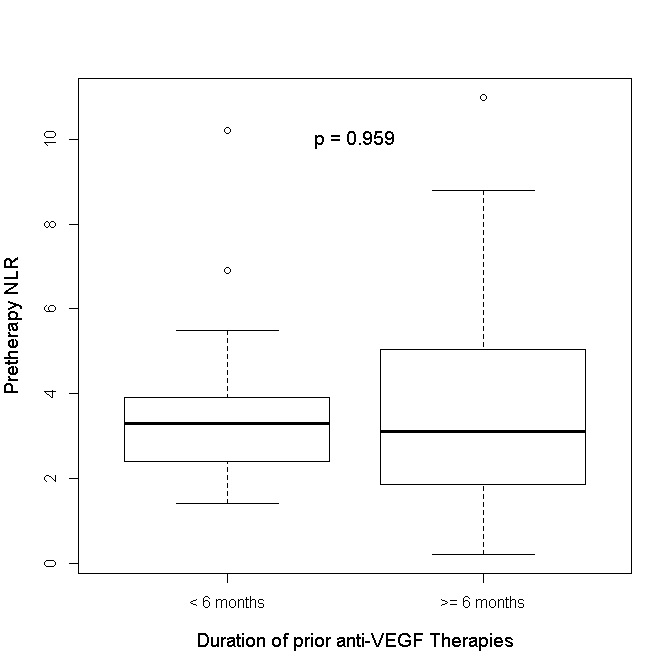
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **PFS\*** | | | |
|  | **Univariable analysis** | | **Multivariable analysis** | |
|  | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| **Heng Prognostic Score** |  |  |  |  |
| **Low** | Reference |  | Reference |  |
| **Int/High^** | 0.779 (0.379,1.6) | 0.496 | 0.886 (0.424,1.851) | 0.748 |
| **Duration of prior anti-VEGF Therapies & Pretherapy NLR** |  |  |  |  |
| **<6 Months & <3** | Reference |  | Reference |  |
| **<6 Months & ≥3** | 2.904 (0.967,8.724) | 0.057 | 2.819 (0.924,8.600) | 0.069 |
| **≥6 Months & <3** | 2.266 (0.75,6.845) | 0.147 | 2.198 (0.716,6.748) | 0.169 |
| **≥6 Months & ≥3** | 6.733 (2.194,20.659) | ***0.001*** | 6.636 (2.153,20.457) | ***0.001*** |

^, Intermediate and high; \*, PD1/PDL1 response rate to progression disease and non-response; #, progression-free survival.

**Table S5. Univariable and multivariable Cox regression analyses of risk factors associated with PFS. Note that two variables ‘Duration of prior anti-VEGF Therapies’ and ‘Pretherapy NLR (with the cutoff value of 3.2 [median])’ are combined.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **PFS\*** | | | |
|  | **Univariable analysis** | | **Multivariable analysis** | |
|  | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| **Heng Prognostic Score** |  |  |  |  |
| **Low** | Reference |  | Reference |  |
| **Int/High^** | 0.779 (0.379,1.6) | 0.496 | 0.916 (0.439,1.908) | 0.814 |
| **Duration of prior anti-VEGF Therapies & Pretherapy NLR** |  |  |  |  |
| **<6 Months & <3** | Reference |  | Reference |  |
| **<6 Months & ≥3** | 2.893 (0.963,8.689) | 0.058 | 2.831 (0.928,8.633) | 0.067 |
| **≥6 Months & <3** | 2.427 (0.818,7.196) | 0.110 | 2.376 (0.79,7.149) | 0.123 |
| **≥6 Months & ≥3** | 6.422 (2.085,19.777) | ***0.001*** | 6.341 (2.047,19.641) | ***0.001*** |

^, Intermediate and high; \*, PD1/PDL1 response rate to progression disease and non-response; #, progression-free survival.



**Figure S1. The boxplot of pretherapy NLR by the duration of prior anti-VEGF therapies**. The p-value is calculated using the Kruskal