**Supplementary Materials For**

**Spatiotemporal Response Heterogeneity across Metastatic Lesions Informs Drug Efficacy and Patient Survival in Colorectal Cancer**

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**Supplementary Figures**

**Supplementary Figure 1**. Conceptual workflow of the lesion pattern definition algorithm.

**Supplementary Figure 2**. Individual lesion and total tumor burden growth dynamics.

**Supplementary Figure 3**. The response patterns of metastatic lesions in patients with high or low Gower distance.

**Supplementary Figure 4**. Treatment efficacy in Beva + Chemo versus Chemo only.

**Supplementary Figure 5**. Treatment efficacy in Pani + Chemo versus Chemo only.

**Supplementary Figure 6**. Gower distance in targeted+Chemo versus Chemo only across organs, **Supplementary Figure 7**. Treatment efficacy in patients with *KRAS* mutations versus wild-type.

**Supplementary Figure 8**. The LN or lung metastases responses were not associated with patient survival.

**Supplementary Tables**

**Supplementary Table 1**. Data Source.

**Supplementary Table 2-12**. The mean (standard deviation) and median (interquartile range) of the data analyzed in the figure 2-4.



**Supplementary Figure 1**. **Conceptual workflow of the lesion pattern characterization algorithm.** We developed an algorithm in MATLAB to characterize lesion response patterns and measure the durations of response, stable and relapse phase.



**Supplementary Figure 2**. **Individual lesion and total tumor burden growth dynamics.** Spider plots of individual tumor size (left) and total tumor burden (right) normalized by tumor baseline during the course of treatment.

(A)



(B)





**Supplementary Figure 3**. **The response patterns of metastatic lesions in patients with high Gower distance (A) or low Gower distance (B).** The Gower distances in (A) range from 0.45 to 0.5 (top 10 in our data set) and the Gower distances in (B) all equal to 0. Patient identification number and corresponding treatment were labeled in each subpanel. Lesions in different anatomical sites were labeled in different symbols. The response, stable, and relapse patterns were plotted in red, green, and blue respectively.



**Supplementary Figure 4**. **Treatment efficacy in Beva + Chemo versus Chemo only.** The nadir ratio, last ratio, response duration, stable duration and relapse duration of the total tumor burden at patient-level in the bevacizumab arm (Beva + Chemo) versus chemotherapy only arm (Chemo only).



**Supplementary Figure 5**. **Treatment efficacy in Pani + Chemo versus Chemo only.** The nadir ratio, last ratio, response duration, stable duration and relapse duration of the total tumor burden at patient-level in the panitumumab arm (Pani + Chemo) versus chemotherapy only arm (Chemo only).



**Supplementary Figure 6**. **Gower distance in targeted+Chemo versus Chemo only across organs.** The Gower distance of liver, lung and lymph nodes metastases under targeted therapy plus chemotherapy versus chemotherapy only.

**Supplementary Figure 7**. **Treatment efficacy in the patients with *KRAS* mutations versus wild-type.** The nadir ratio, last ratio, Gower distance, response duration, stable duration and relapse duration of the total tumor burden in the wild-type patients (n = 795) vs *KRAS* mutant patients (n = 593).



**Supplementary Figure 8**. **The LN or lung metastases responses were not associated with patient survival.** Kaplan-Meier curves of the OS in patients with LN metastases (A) or lung metastases (B). The patients were divided into four subgroups in (A): all lesions shrinkage greater than 30% threshold (all > 30%, n = 334); LN lesions shrinkage > 30% while other lesions shrinkage ≤ 30% (LN > 30%, others ≤ 30%; n = 72); LN lesions shrinkage ≤ 30% while other lesions shrinkage > 30% (others >30%, LN ≤ 30%; n = 100); all lesions shrinkage ≤ 30% (all ≤ 30%, n = 330). The patients in (B) were divided in similar subgroups: all > 30% (n = 190); lung > 30%, others ≤ 30% (n = 49); others >30%, lung ≤ 30% (n = 46); all ≤ 30% (n = 237).

**Supplementary Data Tables**.

**Supplementary Table 1**. **Data Source.** Descriptive information about the five randomized clinical trials in metastatic colorectal cancer collected from Project Data Sphere.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Experimental agent being tested** | **Control treatment** | **Patients included (No.)** | **Masking Method** | **Study phase** | **Study Start date** | **Study end date** | **ClinicalTrial.gov identifier** | **Follow-up visit** |
| Amgen 2006 263 | Panitumumab plus FOLFIRI | FOLFIRI | 844 | Open Label | 3 | June 2006 | November 2010 | NCT00339183 | Safety follow-up assessment 30 days ± 3days |
| Amgen 2006 264  (PRIME) | FOLFOX plus Panitumumab | FOLFOX | 884 | Open Label | 3 | August 2006 | March 2013 | NCT00364013 |
| Amgen 2005 262  (PACCE) | Bevacizumab plus Panitumumab plus chemotherapy | Bevacizumab plus chemotherapy | 748 | Open Label | 3 | June 2005 | May 2009 | NCT00115765 | Safety follow-up visit for 4 weeks and long-term follow-up every 12 weeks until necessary OS events |
| SanofiU 2002 137  (XENOX) | FOLFOX plus Xaliproden | FOLFOX | 130 | Double blinded | 3 | July 2002 | May 2004 | NCT00272051 | Followed every two months until progression or for 13 months after their first dose of study drug |
| SanofiU 2005 136 | FOLFOX plus Xaliproden | FOLFOX | 196 | Double blinded | 3 | December 2005 | October 2009 | NCT00305188 |

**Supplementary Table 2**. The mean (standard deviation) and the median (interquartile range) of the Gower distances at lesion-level across anatomical sites.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Organ (No.) | Mean (sd) | Median (IQR) | Organ (No.) | Mean (sd) | Median (IQR) |
| Abdomen (399) | 0.27 (0.12) | 0.26 (0.14) | Bone (166) | 0.27 (0.13) | 0.27 (0.15) |
| GI (130) | 0.28 (0.14) | 0.28 (0.18) | Liver (7,449) | 0.25 (0.12) | 0.23 (0.14) |
| Lungs (1,169) | 0.25 (0.11) | 0.23 (0.14) | Lymph Nodes (1,833) | 0.26 (0.12) | 0.24 (0.15) |
| Other (258) | 0.25 (0.13) | 0.23 (0.15) |  |  |  |

**Supplementary Table 3**. The mean (standard deviation) and the median (interquartile range) of the Gower distances at patient-level across treatment types.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Treatment (No.) | Mean (sd) | Median (IQR) | Treatment (No.) | Mean (sd) | Median (IQR) |
| Targeted+Chemo (1,614) | 0.22 (0.12) | 0.23 (0.13) | Chemo (1,188) | 0.23 (0.12) | 0.24 (0.13) |
| Beva+Chemo (377) | 0.22 (0.12) | 0.23 (0.13) | Beva+Chemo+Pani (371) | 0.22 (0.12) | 0.24 (0.13) |
| FOLFIRI (419) | 0.22 (0.11) | 0.23 (0.13) | FOLFIRI+Pani (425) | 0.23 (0.12) | 0.24 (0.13) |
| FOLFOX (769) | 0.23 (0.12) | 0.25 (0.13) | FOLFOX+Pani (441) | 0.21 (0.12) | 0.22 (0.13) |

**Supplementary Table 4.** The mean (standard deviation) and the median (interquartile range) of the response pattern parameters at patient-level in the bevacizumab arm (Beva+Chemo) vs chemotherapy arm (Chemo only). The durations were added with one to avoid zero values in logarithmic plots in all the tables below.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Beva+Chemo (n = 377) | | Chemo only (n = 1,188) | |
|  | Mean (sd) | Median (IQR) | Mean (sd) | Median (IQR) |
| Nadir Ratio | 0.63 (0.33) | 0.62 (0.35) | 0.74 (0.36) | 0.75 (0.50) |
| Last Ratio | 0.79 (0.53) | 0.76 (0.42) | 0.89 (0.42) | 0.91 (0.48) |
| Gower distance | 0.22 (0.12) | 0.23 (0.13) | 0.23 (0.12) | 0.24 (0.13) |
| Response duration | 126 (141) | 93 (188) | 78 (125) | 1 (129) |
| Stable duration | 151 (137) | 110 (146) | 121 (119) | 100 (117) |
| Relapse duration | 50 (88) | 1 (86) | 41 (61) | 1 (64) |

**Supplementary Table 5.** The mean (standard deviation) and the median (interquartile range) of the lesion-level nadir ratios in the bevacizumab arm (Beva+Chemo) vs chemotherapy arm (Chemo only).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Beva+Chemo (n = 1,634) | | | Chemo only (n = 4,764) | | |
| Organ (No.) | Mean (sd) | Median (IQR) | Organ (No.) | Mean (sd) | Median (IQR) |
| Abdomen (63) | 0.58 (0.28) | 0.56 (0.40) | Abdomen (170) | 0.89 (0.33) | 0.92 (0.40) |
| Bone (8) | 0.62 (0.27) | 0.63 (0.42) | Bone (91) | 0.85 (0.33) | 0.88 (0.37) |
| GI (10) | 0.71 (0.28) | 0.72 (0.44) | GI (65) | 0.76 (0.29) | 0.81 (0.46) |
| Liver (1,031) | 0.60 (0.29) | 0.58 (0.39) | Liver (3,128) | 0.72 (0.39) | 0.71 (0.57) |
| Lungs (146) | 0.71 (0.23) | 0.73 (0.28) | Lungs (513) | 0.73 (0.31) | 0.79 (0.44) |
| Lymph Nodes (353) | 0.64 (0.23) | 0.66 (0.38) | Lymph Nodes (646) | 0.71 (0.33) | 0.74 (0.45) |
| Other (23) | 0.72 (0.26) | 0.69 (0.48) | Other (151) | 0.81 (0.36) | 0.86 (0.40) |

**Supplementary Table 6.** The mean (standard deviation) and the median (interquartile range) of the lesion-level Gower distances in the bevacizumab arm (Beva+Chemo) vs chemotherapy arm (Chemo only).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Beva+Chemo (n = 1,634) | | | Chemo only (n = 4,764) | | |
| Organ (No.) | Mean (sd) | Median (IQR) | Organ (No.) | Mean (sd) | Median (IQR) |
| Abdomen (63) | 0.26 (0.13) | 0.29 (0.11) | Abdomen (170) | 0.26 (0.12) | 0.25 (0.12) |
| Bone (8) | 0.33 (0.10) | 0.36 (0.16) | Bone (91) | 0.28 (0.13) | 0.28 (0.16) |
| GI (10) | 0.26 (0.13) | 0.29 (0.14) | GI (65) | 0.27 (0.14) | 0.27 (0.18) |
| Liver (1,031) | 0.24 (0.11) | 0.22 (0.13) | Liver (3,128) | 0.25 (0.12) | 0.24 (0.14) |
| Lungs (146) | 0.25 (0.12) | 0.24 (0.16) | Lungs (513) | 0.24 (0.12) | 0.22 (0.14) |
| Lymph Nodes (353) | 0.26 (0.11) | 0.25 (0.15) | Lymph Nodes (646) | 0.26 (0.13) | 0.24 (0.16) |
| Other (23) | 0.22 (0.11) | 0.23 (0.13) | Other (151) | 0.25 (0.13) | 0.22 (0.16) |

**Supplementary Table 7.** The mean (standard deviation) and the median (interquartile range) of the lesion-level response pattern parameters in liver, lung and LN metastases in the bevacizumab arm (Beva+Chemo).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Liver (n = 1,031) | | Lungs (n = 146) | | Lymph Nodes (n = 353) | |
|  | Mean (sd) | Medina (IQR) | Mean (sd) | Medina (IQR) | Mean (sd) | Medina (IQR) |
| Nadir Ratio | 0.60 (0.29) | 0.58 (0.39) | 0.71 (0.23) | 0.73 (0.28) | 0.64 (0.23) | 0.66 (0.38) |
| Last Ratio | 0.76 (0.44) | 0.72 (0.48) | 0.89 (0.36) | 0.85 (0.39) | 0.74 (0.28) | 0.75 (0.37) |
| Gower distance | 0.24 (0.11) | 0.22 (0.13) | 0.25 (0.12) | 0.24 (0.16) | 0.26 (0.11) | 0.25 (0.15) |
| Response duration | 109 (116) | 92 (175) | 54 (87) | 1 (91) | 78 (96) | 78 (113) |
| Stable duration | 173 (132) | 159 (154) | 216 (139) | 186 (235) | 223 (161) | 185 (226) |
| Relapse duration | 37 (71) | 1 (54) | 33 (79) | 1 (0) | 25 (69) | 1 (0) |

**Supplementary Table 8.** The mean (standard deviation) and the median (interquartile range) of the lesion-level response pattern parameters in liver, lung and LN metastases in the chemotherapy arm (Chemo Only).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Liver (n = 3,128) | | Lungs (n = 513) | | Lymph Nodes (n = 646) | |
|  | Mean (sd) | Medina (IQR) | Mean (sd) | Medina (IQR) | Mean (sd) | Medina (IQR) |
| Nadir Ratio | 0.72 (0.39) | 0.71 (0.57) | 0.73 (0.31) | 0.79 (0.44) | 0.71 (0.33) | 0.74 (0.45) |
| Last Ratio | 0.88 (0.44) | 0.89 (0.63) | 0.87 (0.36) | 0.91 (0.44) | 0.81 (0.38) | 0.84 (0.43) |
| Gower distance | 0.25 (0.12) | 0.24 (0.14) | 0.24 (0.12) | 0.22 (0.14) | 0.26 (0.13) | 0.24 (0.16) |
| Response duration | 74 (105) | 1 (124) | 45 (72) | 1 (72) | 62 (113) | 1 (79) |
| Stable duration | 116 (119) | 92 (109) | 142 (105) | 122 (122) | 153 (146) | 118 (128) |
| Relapse duration | 39 (58) | 1 (63) | 23 (42) | 1 (52) | 19 (44) | 1 (0) |

**Supplementary Table 9.** The mean (standard deviation) and the median (interquartile range) of the response pattern parameters at patient-level in the panitumumab arm (Pani+Chemo) vs chemotherapy arm (Chemo only).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Pani+Chemo (n = 866) | | Chemo only (n = 1,188) | |
|  | Mean (sd) | Median (IQR) | Mean (sd) | Median (IQR) |
| Nadir Ratio | 0.68 (0.36) | 0.66 (0.49) | 0.74 (0.36) | 0.75 (0.50) |
| Last Ratio | 0.84 (0.44) | 0.85 (0.54) | 0.89 (0.42) | 0.91 (0.48) |
| Gower distance | 0.22 (0.12) | 0.23 (0.13) | 0.23 (0.12) | 0.24 (0.13) |
| Response duration | 100 (139) | 63 (147) | 78 (125) | 1 (129) |
| Stable duration | 132 (135) | 113 (123) | 121 (119) | 100 (117) |
| Relapse duration | 49 (77) | 1 (69) | 41 (61) | 1 (64) |

**Supplementary Table 10.** The mean (standard deviation) and the median (interquartile range) of the lesion-level nadir ratios across anatomical sites in the panitumumab arm (Pani + Chemo) vs chemotherapy arm (Chemo only).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Pani+Chemo (n = 3,500) | | | Chemo only (n = 4,764) | | |
| Organ (No.) | Mean (sd) | Median (IQR) | Organ (No.) | Mean (sd) | Median (IQR) |
| Abdomen (116) | 0.83 (0.35) | 0.89 (0.43) | Abdomen (170) | 0.89 (0.33) | 0.92 (0.40) |
| Bone (55) | 0.83 (0.28) | 0.82 (0.50) | Bone (91) | 0.85 (0.33) | 0.88 (0.37) |
| GI (44) | 0.66 (0.34) | 0.70 (0.58) | GI (65) | 0.76 (0.29) | 0.81 (0.46) |
| Liver (2,422) | 0.64 (0.37) | 0.60 (0.52) | Liver (3,128) | 0.72 (0.39) | 0.71 (0.57) |
| Lungs (266) | 0.72 (0.24) | 0.69 (0.37) | Lungs (513) | 0.73 (0.31) | 0.79 (0.44) |
| Lymph Nodes (534) | 0.68 (0.29) | 0.70 (0.49) | Lymph Nodes (646) | 0.71 (0.33) | 0.74 (0.45) |
| Other (63) | 0.92 (0.31) | 0.95 (0.36) | Other (151) | 0.81 (0.36) | 0.86 (0.40) |

**Supplementary Table 11.** The mean (standard deviation) and the median (interquartile range) of the lesion-level Gower distances across anatomical sites in the panitumumab arm (Pani + Chemo) vs chemotherapy arm (Chemo only).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Pani+Chemo (n = 3,500) | | | Chemo only (n = 4,764) | | |
| Organ (No.) | Mean (sd) | Median (IQR) | Organ (No.) | Mean (sd) | Median (IQR) |
| Abdomen (116) | 0.27 (0.12) | 0.26 (0.14) | Abdomen (170) | 0.26 (0.12) | 0.25 (0.12) |
| Bone (55) | 0.27 (0.11) | 0.27 (0.13) | Bone (91) | 0.28 (0.13) | 0.28 (0.16) |
| GI (44) | 0.29 (0.15) | 0.32 (0.20) | GI (65) | 0.27 (0.14) | 0.27 (0.18) |
| Liver (2,422) | 0.24 (0.11) | 0.22 (0.14) | Liver (3,128) | 0.25 (0.12) | 0.24 (0.14) |
| Lungs (266) | 0.25 (0.10) | 0.24 (0.12) | Lungs (513) | 0.24 (0.12) | 0.22 (0.14) |
| Lymph Nodes (534) | 0.27 (0.12) | 0.25 (0.15) | Lymph Nodes (646) | 0.26 (0.13) | 0.24 (0.16) |
| Other (63) | 0.26 (0.12) | 0.23 (0.14) | Other (151) | 0.25 (0.13) | 0.22 (0.16) |

**Supplementary Table 12.** The mean (standard deviation) and the median (interquartile range) of the lesion-level response pattern parameters in liver, lung and LN metastases in the panitumumab arm (Pani + Chemo).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Liver (n = 2,422) | | Lungs (n = 266) | | Lymph Nodes (n = 534) | |
|  | Mean (sd) | Median (IQR) | Mean (sd) | Median (IQR) | Mean (sd) | Median (IQR) |
| Nadir over baseline | 0.64 (0.37) | 0.60 (0.52) | 0.72 (0.24) | 0.69 (0.37) | 0.68 (0.29) | 0.70 (0.49) |
| Last over baseline | 0.82 (0.45) | 0.80 (0.61) | 0.91 (0.33) | 0.90 (0.41) | 0.80 (0.34) | 0.81 (0.46) |
| Gower distance | 0.24 (0.11) | 0.22 (0.14) | 0.25 (0.10) | 0.24 (0.12) | 0.27 (0.12) | 0.25 (0.15) |
| Response duration | 103 (130) | 68 (146) | 52 (70) | 53 (77) | 65 (92) | 46 (112) |
| Stable duration | 136 (142) | 113 (123) | 152 (99) | 127 (125) | 156 (135) | 119 (135) |
| Relapse duration | 43 (69) | 1 (63) | 42 (77) | 1 (58) | 32 (70) | 1 (49) |