**Supplementary Table S4. Correlative analysis of PFS and OS with the expression of biomarkers using the 25th percentile and median marker distributions as cutpoints: total IR, IR-A, IR-B, and IGF-1R in pooled group and arm A**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Treatment Arm**  **(n)** | **Endpoint** | **Expression** | **Median  Survival in  Months**  **(95% CI)** | **HR  (95% CI)** | **High vs Low**  **(P-value)** | **Survival  Rates (%)**  **(12 months)** | **Survival Rates (%)**  **(24 months)** |
| Total IR (median cutpoint) | Pooled  (n = 59) | PFS | Higha | 2.0 (1.9, 3.1) | 1.38 (0.76, 2.50) | 0.2781 |  |  |
|  | Low | 3.4 (1.9, 5.4) |  |  |
| OS | High | NA (11.5, NA) | 1.65 (0.67, 4.05) | 0.2663 | 64.9 | 55.7 |
|  | Low | NA (20.3, NA) | 75.2 | 60.2 |
| Arm A  (n = 40) | PFS | High | 2.0 (1.7, 3.1) | 1.31 (0.61, 2.78) | 0.4808 |  |  |
|  | Low | 3.7 (1.8, 5.5) |  |  |
| OS | High | 13.9 (3.3, NA) | 2.50 (0.92, 6.85) | 0.0643 | 51.3 | 38.0 |
|  | Low | NA (8.6, NA) | 73.7 | 55.3 |
| IR-A  (median cutpoint) | Pooled  (n = 59) | PFS | High | 2.0 (1.9, 3.7) | 1.24 (0.69, 2.24) | 0.4600 |  |  |
|  | Low | 3.4 (1.8, 4.4) |  |  |
| OS | High | NA (11.5, NA) | 1.45 (0.60, 3.50) | 0.4080 | 63.7 | 57.9 |
|  | Low | NA (20.3, NA) | 76.1 | 57.8 |
| Arm A  (n = 40) | PFS | High | 2.0 (1.9, 3.8) | 0.85 (0.40, 1.79) | 0.6628 |  |  |
|  | Low | 2.0 (1.7, 5.5) |  |  |
| OS | High | 15.9 (4.3, NA) | 1.57 (0.60, 4.12) | 0.3586 | 54.0 | 47.2 |
|  | Low | 20.3 (8.6, NA) | 72.2 | 43.7 |
| IR-B  (median cutpoint) | Pooled  (n = 59) | PFS | High | 2.0 (1.9, 3.6) | 1.19 (0.66, 2.15) | 0.5475 |  |  |
|  | Low | 3.1 (1.9, 3.8) |  |  |
| OS | High | 15.9 (8.8, NA) | 2.84 (1.09, 7.40) | 0.0255 | 57.9 | 49.4 |
|  | Low | NA (20.3, NA) | 82.2 | 65.7 |
| Arm A  (n = 40) | PFS | High | 2.0 (1.7, 3.1) | 1.32 (0.63, 2.75) | 0.4550 |  |  |
|  | Low | 3.7 (1.9, 5.5) |  |  |
| OS | High | 11.5 (3.3, 15.9) | 5.3 (1.74, 16.68) | 0.0012 | 40.5 | 27.8 |
|  | Low | NA (20.3, NA) | 83.8 | 62.9 |
| IGF-1R  (median cutpoint) | Pooled  (n = 57) | PFS | High | 3.1 (1.8, 3.7) | 1.25(0.68, 2.29) | 0.4596 |  |  |
|  | Low | 2.0 (1.9, 5.4) |  |  |
| OS | High | NA (10.8, NA) | 1.25 (0.51, 3.07) | 0.6286 | 63.6 | 63.6 |
|  | Low | NA (15.9, NA) | 77.6 | 51.4 |
| Arm A  (n = 39) | PFS | High | 3.1 (1.8, 3.7) | 1.24 (0.59, 2.62) | 0.5605 |  |  |
|  | Low | 2.0 (1.7, 5.5) |  |  |
| OS | High | NA (4.2, NA) | 1.11 (0.41, 3.00) | 0.8294 | 57.8 | 57.8 |
|  | Low | 20.3 (8.8, NA) | 69.6 | 38.1 |
| Total IR  (25th percentile cutpoint) | Pooled  (n = 59) | PFS | High | 2.0 (1.9, 3.7) | 1.12 (0.58, 2.16) | 0.7379 |  |  |
|  | Low | 3.4 (1.2, 5.4) |  |  |
| OS | High | NA (13.9, NA) | 1.47 (0.49, 4.40) | 0.4895 | 67.2 | 61.5 |
|  | Low | 20.3 (8.6, NA) | 77.8 | 38.9 |
| Arm A  (n = 40) | PFS | High | 2.0 (1.9, 3.8) | 0.83 (0.37, 1.87) | 0.6538 |  |  |
|  | Low | 3.4 (1.2, 3.7) |  |  |
| OS | High | 15.9 (4.5, NA) | 2.00 (0.57, 6.98) | 0.2670 | 56.6 | 48.4 |
|  | Low | 20.3 (8.0, 20.3) | 77.8 | NAb |
| IR-A  (25th percentile cutpoint) | Pooled  (n =59) | PFS | High | 2.0 (1.9, 3.6) | 1.30 (0.67, 2.52) | 0.4316 |  |  |
|  | Low | 3.7 (1.7, 5.4) |  |  |
| OS | High | NA (13.9, NA) | 1.49 (0.50, 4.47) | 0.4708 | 67.2 | 61.3 |
|  | Low | 20.3 (8.6, NA) | 77.8 | 38.9 |
| Arm A  (n =40) | PFS | High | 2.0 (1.9, 3.8) | 0.99 (0.43, 2.27) | 0.9761 |  |  |
|  | Low | 3.4 (1.2, 5.5) |  |  |
| OS | High | 15.9 (4.5, NA) | 1.75 (0.50, 6.10) | 0.3732 | 58.1 | 49.7 |
|  | Low | 20.3 (8.0, 20.3) | 75.0 | NAb |
| IR-B  (25th percentile cutpoint) | Pooled  (n =59) | PFS | High | 2.0 (1.9, 3.6) | 0.91 (0.47, 1.74) | 0.7644 |  |  |
|  | Low | 3.4 (1.8, 3.7) |  |  |
| OS | High | NA (13.9, NA) | 1.79 (0.52, 6.13) | 0.3450 | 67.8 | 53.1 |
|  | Low | NA (8.0, NA) | 77.1 | 77.1 |
| Arm A  (n =40) | PFS | High | 2.0 (1.7, 3.1) | 1.22 (0.55, 2.73) | 0.6197 |  |  |
|  | Low | 3.7 (1.9, 5.5) |  |  |
| OS | High | 15.9 (4.5, NA) | 6.6 (0.88, 50.03) | 0.0343 | 54.4 | 34.1 |
|  | Low | NA (8.0, NA) | 87.5 | 87.5 |
| IGF-1R (25th percentile cutpoint) | Pooled  (n =57) | PFS | High | 2.0 (1.9, 3.6) | 1.73 (0.86, 3.46) | 0.1151 |  |  |
|  | Low | 5.4 (1.7, 14.5) |  |  |
| OS | High | NA (11.5, NA) | 2.44 (0.71, 8.40) | 0.1432 | 62.4 | 59.7 |
|  | Low | NA (15.9, NA) | 93.3 | 56.0 |
| Arm A  (n =39) | PFS | High | 2.0 (1.9, 3.4) | 2.52 (1.04, 6.08) | 0.0322 |  |  |
|  | Low | 5.5 (1.7, 14.5) |  |  |
| OS | High | 13.9 (8.0, NA) | 2.93 (0.83, 10.39) | 0.0818 | 51.7 | 47.0 |
|  | Low | NA (15.9, NA) | 91.7 | 53.5 |

Abbreviations: Arm A = cixutumumab + anti-estrogen; CI = confidence interval; HR = hazard ratio; n = number of patients; NA = not applicable; OS = overall survival; PFS = progression-free survival; Pooled group = Arm A (cixutumumab + antiestrogen) + Arm B (cixutumumab monotherapy).

aFor the median cutpoint, high expression refers to expression levels equal to or above the median, low expression refers to expression levels below the median.

bThe time of 24 months is beyond the last censored time observation and is therefore undefined.