**Table S1.** List of the antibodies used for the immunohistochemical assay

| Antibody | Clone | Company | Dilution |
|---|---|---|---|
| PD-1 | NAT105 | Roche | Ready to use |
| PD-L1 | 22C3 | Dako | 1:50 |
| c-Met | SP44 | Roche | Ready to use |
| Phospho-4e-BP1 | Thr37/46 | Cell Signaling | 1:50 |
| Phospho-S6R | Ser235/236 | Cell Signaling | 1:50 |
| Phospho-m-Tor | Ser2448 | Cell Signaling | 1:50 |

**Table S2.** Clinical characteristics of the study population

| Clinical variables | N° of patients | % of patients* |
|---|---|---|
| **Gender** | | |
| M | 15 | 60% |
| F | 10 | 40% |
| **Stage at diagnosis** | | |
| I | 11 | 44% |
| II | 6 | 24% |
| III | 4 | 16% |
| IV | 4 | 16% |
| **Type of nephrectomy** | | |
| Partial | 1 | 4% |
| Radical | 24 | 96% |
| with lymphadenectomy | 1 | 4% |
| with adrenalectomy | 4 | 16% |

| | | |
|---|---|---|
| **Intent of nephrectomy** | | |
| palliative (cytoreduction) | 4 | 16% |
| curative | 21 | 84% |
| **Systemic treatment after nephrectomy** | | |
| Any | 20 | 80% |
| Adjuvant | 3 | 12% |
| I line | 2 | 8% |
| **Type of pulmonary surgery** | | |
| metastasectomy | 11 | 44% |
| wedge resection | 9 | 36% |
| lobectomy | 4 | 16% |
| bilobectomy | 1 | 4% |
| with lymphadenectomy | 6 | 24% |
| **Relapse after pulmonary surgery** | | |
| Yes | 11 | 44% |
| No | 5 | 20% |
| Unknown | 9 | 36% |
| **Systemic therapy after relapse** | | |
| Yes | 10 | 40% |
| No | 5 | 20% |
| Unknown | 10 | 40% |

* The percentage was evaluated based on the total number of patients which were evaluable for the parameter.

** The median age of patients was 65 years (range 55–78)

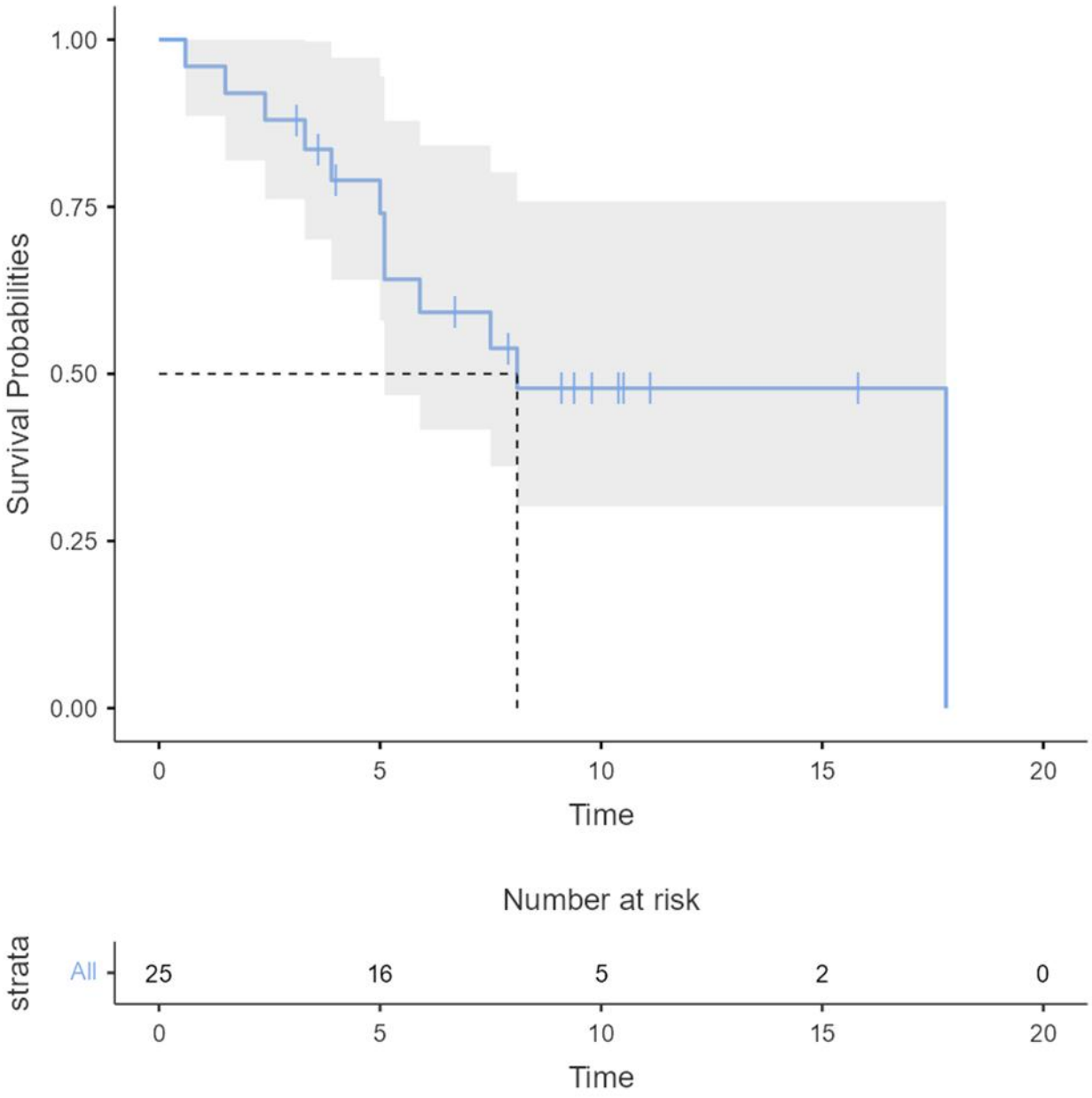


**Figure S1.** Overall survival of the study population from the first diagnosis of renal cancer (coincident with the time of nephrectomy in all cases)

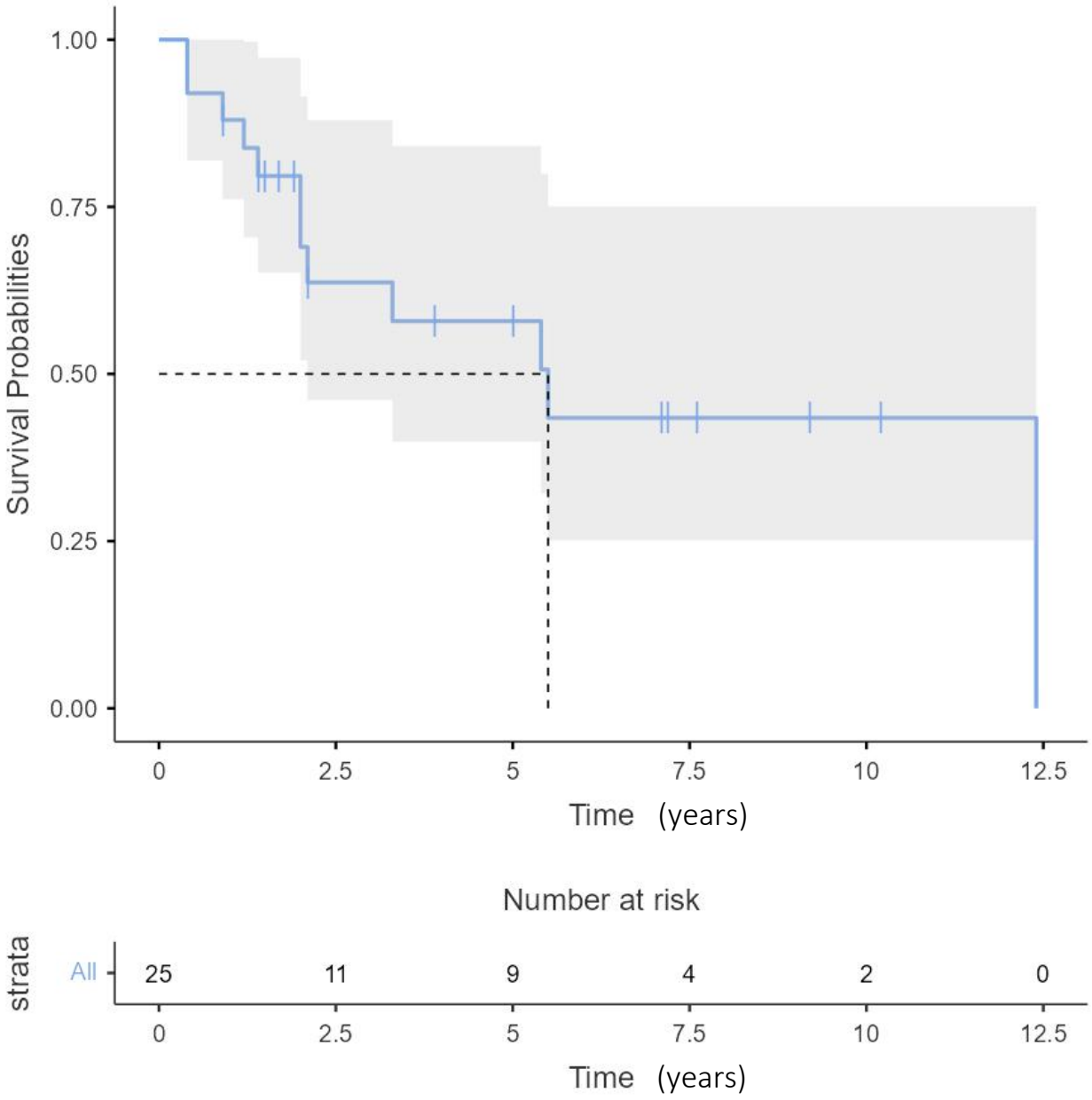


**Figure S2.** Overall survival of the study population from pulmonary metastasectomy

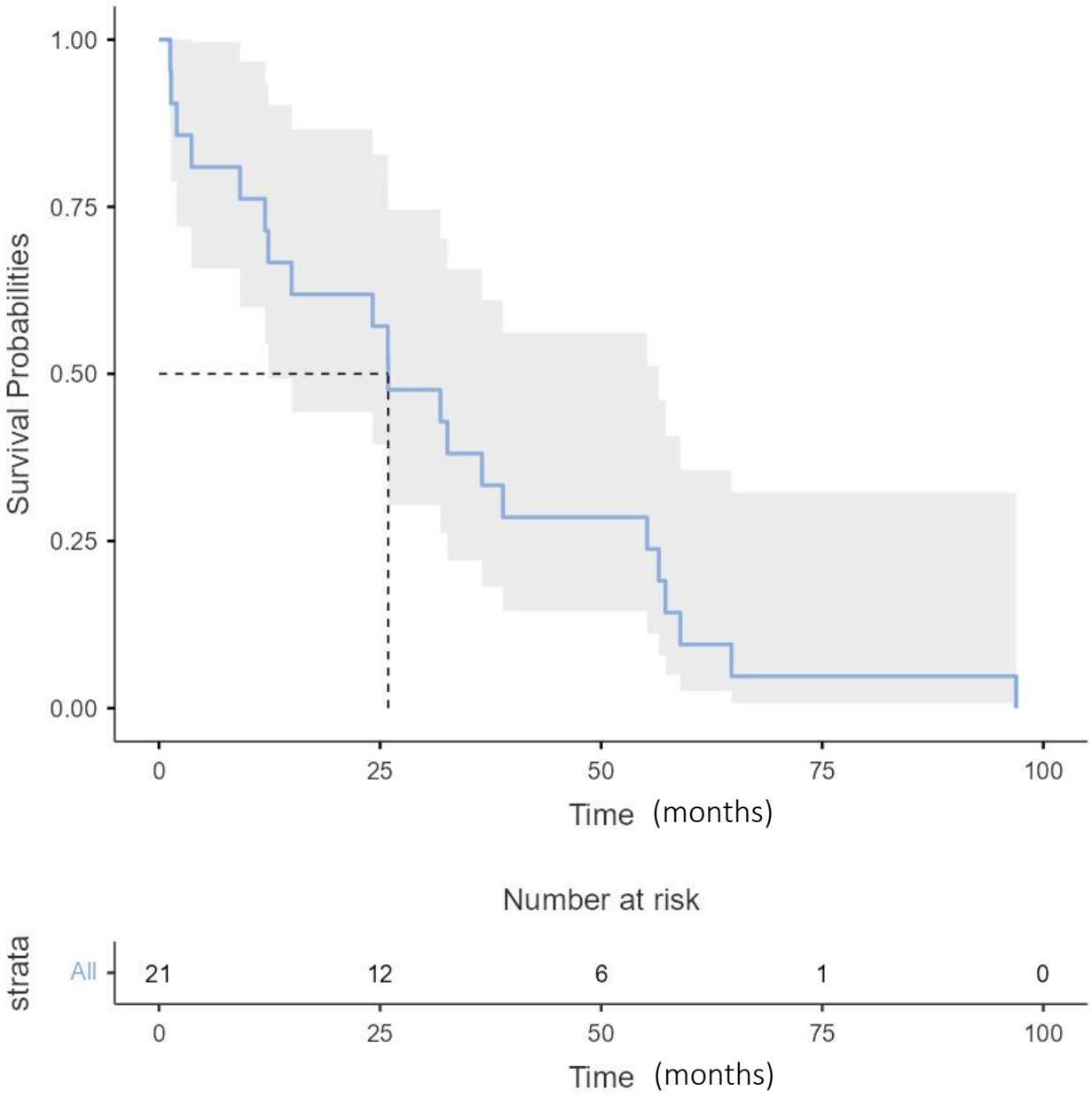


**Figure S3.** Relapse-free survival from nephrectomy in the overall population

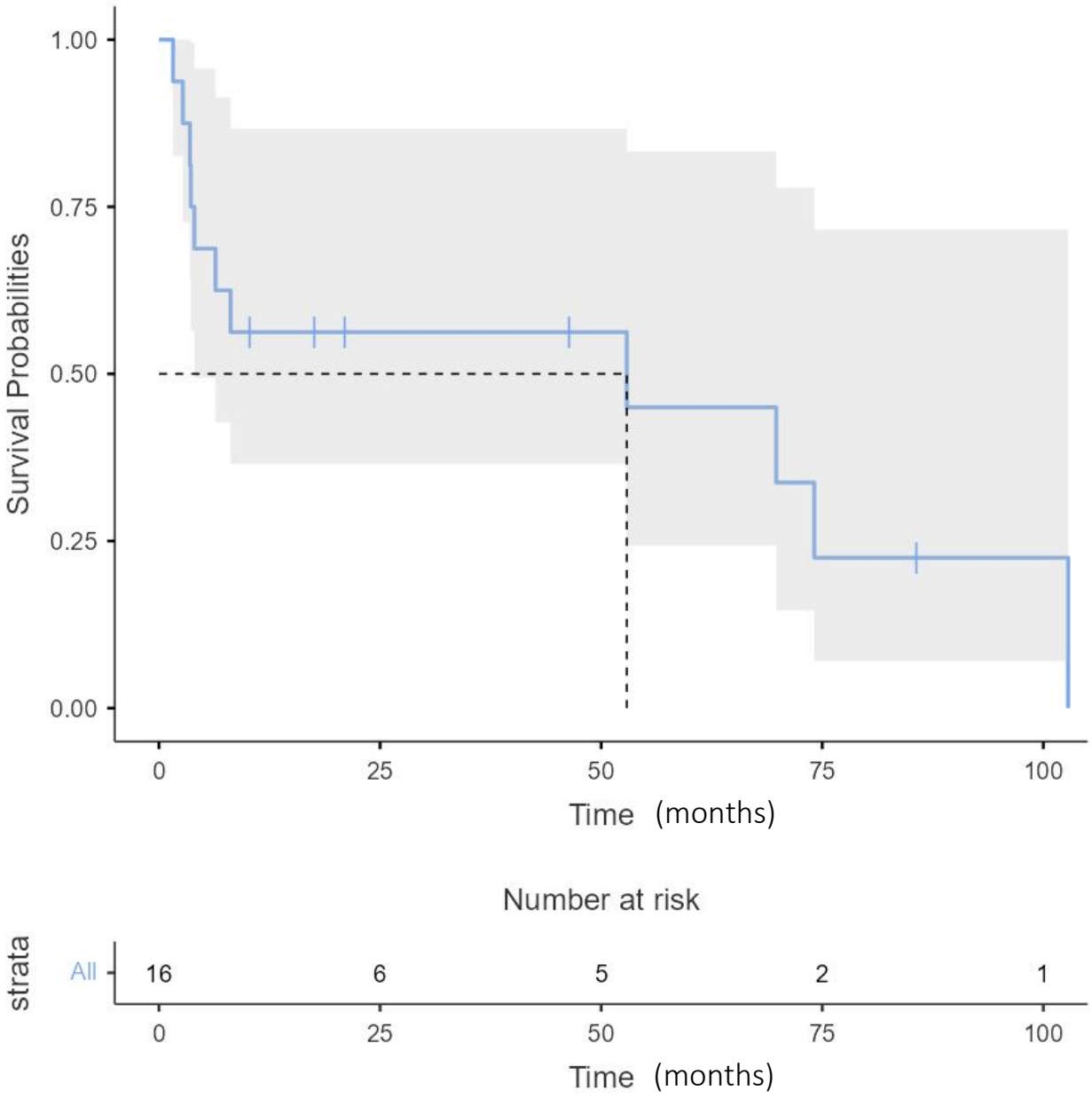


**Figure S4.** Relapse-free survival from pulmonary metastasectomy in the evaluable population

**Table S3.** Intratumor heterogeneity (ITH) between qualitative expression of biomarkers belonging to MET and mTOR pathways in the primary tumor (T) and the respective pulmonary metastasis (M). The ITH grade was low for the MET pathway (only one case with a heterogeneous expression) but instead relatively high for the mTOR pathway (15 cases of ITH). Among the different biomarkers, S6RP was the most frequently heterogeneous (14 discordant cases). Heterogeneous cases (for at least one parameter) are reported in red

| Case N° | MET T | MET M | 4EBP1 T | 4EBP1 M | S6RP T | S6RP M | mTOR T | mTOR M |
|---|---|---|---|---|---|---|---|---|
| 1 | + | + | + | + | + | + | + | + |
| 2 | - | + | + | + | - | + | + | + |
| 3 | + | + | + | + | - | - | - | - |
| 4 | + | + | + | + | - | - | + | + |
| 5 | + | + | + | + | - | + | - | - |
| 6 | + | + | + | + | + | + | + | + |
| 7 | + | + | + | + | - | - | + | + |
| 8 | + | + | - | + | - | + | + | + |
| 9 | + | + | + | + | - | + | + | - |
| 10 | + | + | + | + | - | + | - | + |
| 11 | + | + | + | + | - | + | + | + |
| 12 | + | + | - | + | - | + | + | - |
| 13 | - | - | - | + | - | + | + | + |
| 14 | + | + | + | + | - | + | + | + |
| 15 | + | + | + | + | - | + | + | + |
| 16 | + | + | + | + | - | + | + | + |
| 17 | + | + | + | + | + | + | + | - |
| 18 | + | + | + | + | - | + | + | + |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 19 | + | + | + | + | + | - | + | + |
| 20 | + | + | + | + | + | + | + | + |
| 21 | + | + | + | + | - | - | + | + |
| 22 | + | + | + | + | - | - | - | + |
| 23 | + | + | + | + | - | + | - | - |
| 24 | + | + | + | + | + | + | + | + |
| 25 | + | + | + | + | - | - | + | + |

**Table S4.** Intratumor heterogeneity (ITH) between quantitative expression of biomarkers belonging to MET and mTOR pathways in the primary tumor (T) and the respective pulmonary metastasis (M). The ITH grade regarding the intensity of protein expression was widely high for all biomarkers and cases. Heterogeneous cases (for at least one parameter) are reported in red. Only one case demonstrated quantitative homogeneity for all biomarkers

| Case N° | MET T | MET M | 4EBP1 T | 4EBP1 M | S6RP T | S6RP M | mTOR T | mTOR M |
|---|---|---|---|---|---|---|---|---|
| 1 | 3 | 3 | 2 | 3 | 2 | 2 | 3 | 1 |
| 2 | 0 | 1 | 1 | 1 | 0 | 1 | 3 | 1 |
| 3 | 1 | 2 | 3 | 2 | 0 | 1 | 0 | 0 |
| 4 | 1 | 2 | 2 | 2 | 0 | 0 | 1 | 1 |
| 5 | 2 | 3 | 3 | 3 | 0 | 1 | 0 | 0 |
| 6 | 2 | 2 | 3 | 1 | 1 | 3 | 3 | 3 |
| 7 | 2 | 3 | 3 | 3 | 0 | NE | 3 | 2 |
| 8 | 2 | 3 | 0 | 3 | 0 | 3 | 3 | 3 |
| 9 | 1 | 3 | 1 | 3 | 0 | 3 | 2 | 0 |
| 10 | 1 | 2 | 1 | 3 | 0 | 2 | 0 | 1 |
| 11 | 1 | 2 | 1 | 3 | 0 | 2 | 3 | 2 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 12 | 1 | 3 | 0 | 3 | 0 | 1 | 3 | 0 |
| 13 | 0 | 0 | 0 | 2 | 0 | 1 | 2 | 1 |
| 14 | 3 | 3 | 2 | 3 | 0 | 3 | 2 | 3 |
| 15 | 1 | 1 | 3 | 3 | 0 | 1 | 3 | 1 |
| 16 | 1 | 2 | 2 | 3 | 0 | 2 | 2 | 1 |
| 17 | 1 | 3 | 1 | 3 | 1 | 1 | 3 | 0 |
| 18 | 1 | 3 | 2 | 3 | 0 | 2 | 2 | 3 |
| 19 | 2 | 1 | 1 | 2 | 2 | 0 | 3 | 1 |
| 20 | 2 | 3 | 2 | 3 | 2 | 3 | 2 | 1 |
| 21 | 2 | 3 | 1 | 3 | 0 | 0 | 1 | 1 |
| 22 | 3 | 3 | 3 | 3 | 0 | 0 | 0 | 1 |
| 23 | 3 | 3 | 3 | 3 | 0 | 3 | 0 | 0 |
| 24 | 1 | 2 | 3 | 2 | 1 | 1 | 3 | 1 |
| 25 | 1 | 3 | 1 | 3 | 0 | 0 | 3 | 3 |

NE = not evaluable