**Supplementary Table 1. Patient demographic and clinical characteristics**

**(A) METEOR**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **CABOZANTINIB**  **(N=150)** | | **EVEROLIMUS**  **(N=156)** | | **Total**  **(N=306)** | |
|  | N | % | N | % | N | % |
| **Gender** |  |  |  |  |  |  |
| Female | 28 | 19 | 45 | 29 | 73 | 24 |
| Male | 122 | 81 | 111 | 71 | 233 | 76 |
| **Geographic region** |  |  |  |  |  |  |
| Europe | 84 | 56 | 88 | 56 | 172 | 56 |
| North America | 52 | 35 | 50 | 32 | 102 | 33 |
| Other | 14 | 9 | 18 | 12 | 32 | 10 |
| **Race** |  |  |  |  |  |  |
| White | 120 | 80 | 120 | 77 | 240 | 78 |
| Asian | 5 | 3 | 10 | 6 | 15 | 5 |
| Black | 2 | 1 | 2 | 1 | 4 | 1 |
| Other | 14 | 9 | 9 | 6 | 23 | 8 |
| Not reported | 9 | 6 | 15 | 10 | 24 | 8 |
| **ECOG performance status** |  |  |  |  |  |  |
| 0 | 107 | 71 | 97 | 62 | 204 | 67 |
| 1 | 43 | 29 | 59 | 38 | 102 | 33 |
| **MSKCC risk factors** |  |  |  |  |  |  |
| 0 | 72 | 48 | 68 | 44 | 140 | 46 |
| 1 | 64 | 43 | 67 | 43 | 131 | 43 |
| 2 or 3 | 14 | 9 | 21 | 13 | 35 | 11 |
| **IMDC risk group** |  |  |  |  |  |  |
| Favorable | 31 | 21 | 33 | 21 | 64 | 21 |
| Intermediate | 97 | 65 | 101 | 65 | 198 | 65 |
| Poor | 22 | 15 | 22 | 14 | 44 | 14 |
| **Bone metastasis** |  |  |  |  |  |  |
| No | 114 | 76 | 124 | 79 | 238 | 78 |
| Yes | 36 | 24 | 32 | 21 | 68 | 22 |
| **Liver metastasis** |  |  |  |  |  |  |
| No | 111 | 74 | 105 | 67 | 216 | 71 |
| Yes | 39 | 26 | 51 | 33 | 90 | 29 |
| **Prior nephrectomy** |  |  |  |  |  |  |
| No | 14 | 9 | 19 | 12 | 33 | 11 |
| Yes | 136 | 91 | 137 | 88 | 273 | 89 |
| **Prior VEGFR-target TKI Therapy** |  |  |  |  |  |  |
| 1 | 111 | 74 | 112 | 72 | 223 | 73 |
| 2 or more | 39 | 26 | 44 | 28 | 83 | 27 |

**(B) CABOSUN**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **CABOZANTINIB**  **(N=61)** | | **SUNITINIB**  **(N=49)** | | **Total**  **(N=110)** | |
|  | N | % | N | % | N | % |
| **Gender** |  |  |  |  |  |  |
| Female | 10 | 16 | 15 | 31 | 25 | 23 |
| Male | 51 | 84 | 34 | 69 | 85 | 77 |
| **ECOG performance status** |  |  |  |  |  |  |
| 0 | 30 | 49 | 24 | 49 | 54 | 49 |
| 1 | 25 | 41 | 20 | 41 | 45 | 41 |
| 2 | 6 | 10 | 5 | 10 | 11 | 10 |
| **IMDC risk group** |  |  |  |  |  |  |
| Intermediate | 52 | 85 | 36 | 73 | 88 | 80 |
| Poor | 9 | 15 | 13 | 27 | 22 | 20 |
| **Bone metastasis** |  |  |  |  |  |  |
| No | 37 | 61 | 30 | 61 | 67 | 61 |
| Yes | 24 | 39 | 19 | 39 | 43 | 39 |
| **Liver metastasis** |  |  |  |  |  |  |
| No | 49 | 80 | 36 | 73 | 85 | 77 |
| Yes | 12 | 20 | 13 | 27 | 25 | 23 |
| **Prior nephrectomy** |  |  |  |  |  |  |
| No | 12 | 20 | 12 | 24 | 24 | 22 |
| Yes | 49 | 80 | 37 | 76 | 86 | 78 |

**Supplementary Table 2. Associations of PD-L1 expression with response to therapy**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **METEOR (N=306)** | | | | | **CABOSUN (N=110)** | | | **Combining two trials (N=416)**  **Adjusted odds ratio\***  **(95% CI)** | |
|  | **Total** | **N(%)**  **ORR** | | **N(%)**  **DCR** | | **Total** | **N(%)**  **ORR** | **N(%)**  **DCR** | **For ORR** | **For DCR** |
| **PD-L1 expression in TC (≥1% cutoff)** |  |  | |  | |  |  |  |  |  |
| PD-L1(-) | 218 | 25(11%) | | 163(75%) | | 85 | 14(16%) | 57(67%) | 1(reference) | 1(reference) |
| PD-L1(+) | 88 | 10(11%) | | 62(70%) | | 25 | 3(12%) | 13(52%) | 1.07(0.53-2.18) | 0.94(0.56-1.56) |
| p-value |  | 0.99 | | 0.48 | |  | 0.76 | 0.24 | 0.85 | 0.80 |
| **PD-L1 expression in IC (≥1% cutoff)** |  |  |  | |  |  |  |  |  |  |
| PD-L1(-) | 122 | 15(12%) | | 95(78%) | | 43 | 6(14%) | 29(67%) | 1(reference) | 1(reference) |
| PD-L1(+) | 179 | 20(11%) | | 127(71%) | | 67 | 11(16%) | 41(61%) | 1.02(0.55-1.90) | 0.75(0.46-1.21) |
| p-value |  | 0.86 | | 0.19 | |  | 0.79 | 0.55 | 0.96 | 0.24 |

ORR: Overall response rate (CR+PR); DCR: Disease control rate (CR+PR+SD)

\*Adjusted for treatment, IMDC risk groups, presence of bone metastases and number of previous VEGFR TKI treatment (0, 1, or ≥2).

**Supplementary Table 3. Treatment comparison on ORR and DCR, subgroup analysis by PD-L1 expression status on tumor cells (TC)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **METEOR (N=306)** | | | | **CABOSUN (N=110)** | | | |
|  | **Cabozantinib** | | **Everolimus** | | **Cabozantinib** | | **Sunitinib** | |
|  | **Total** | **N(%)** | **Total** | **N(%)** | **Total** | **N(%)** | **Total** | **N(%)** |
| **ORR** |  |  |  |  |  |  |  |  |
| **TC (**≥**1% cutoff)** |  |  |  |  |  |  |  |  |
| PD-L1(-) | 112 | 20(18%) | 106 | 5(5%) | 52 | 11(21%) | 33 | 3(9%) |
| PD-L1(+) | 38 | 7(18%) | 50 | 3(6%) | 9 | 1(11%) | 16 | 2(13%) |
| **DCR** |  |  |  |  |  |  |  |  |
| **TC (**≥**1% cutoff)** |  |  |  |  |  |  |  |  |
| PD-L1(-) | 112 | 96(86%) | 106 | 67(63%) | 52 | 41(79%) | 33 | 16(48%) |
| PD-L1(+) | 38 | 33(87%) | 50 | 29(58%) | 9 | 8(89%) | 16 | 5(31%) |

ORR: Overall response rate (CR+PR); DCR: Disease control rate (CR+PR+SD)

**Supplementary Table 4. Treatment comparison on PFS and OS, subgroup analysis by PD-L1 expression status on tumor cells (TC), immune cells (IC) or TC/IC combined scores\*.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **METEOR (N=306)** | | | **CABOSUN (N=110)** | | |
|  | **Cabozantinib versus Everolimus (reference)** | | | **Cabozantinib versus Sunitinib (reference)** | | |
|  | **N** | **PFS HR(95%CI)** | **OS**  **HR(95%CI)** | **N** | **PFS HR(95%CI)** | **OS**  **HR(95%CI)** |
| **TC (**≥**1% cutoff)** |  |  |  |  |  |  |
| PD-L1(-) | 112 vs 106 | 0.46(0.32-0.66) | 0.58(0.38-0.88) | 52 vs 33 | 0.47(0.26-0.86) | 0.71(0.39-1.29) |
| PD-L1(+) | 38 vs 50 | 0.66(0.40-1.11) | 0.82(0.47-1.41) | 9 vs 16 | 0.46(0.18-1.21) | 0.85(0.31-2.31) |
| **IC (**≥**1% cutoff)** |  |  |  |  |  |  |
| PD-L1(-) | 60 vs 62 | 0.44(0.27-0.69) | 0.40(0.22-0.71) | 25 vs 18 | 0.39(0.17-0.86) | 0.82(0.35-1.91) |
| PD-L1(+) | 87 or 92 | 0.55(0.38-0.81) | 0.85(0.56-1.28) | 36 vs 31 | 0.46(0.24-0.88) | 0.61(0.33-1.14) |
| **IC (**≥**5% cutoff)** |  |  |  |  |  |  |
| PD-L1(-) | 101 vs 102 | 0.45(0.32-0.65) | 0.52(0.34-0.78) | 46 vs 32 | 0.34(0.19-0.62) | 0.65(0.35-1.19) |
| PD-L1(+) | 46 vs 52 | 0.67(0.40-1.13) | 0.96(0.54-1.70) | 15 vs 17 | 0.73(0.29-1.85) | 0.81(0.32-2.00) |
| **TC/IC Combined (**≥**1% cutoff)** |  |  |  |  |  |  |
| PD-L1(-) | 64 vs 66 | 0.46(0.29-0.71) | 0.45(0.26-0.77) | 33 vs 19 | 0.44(0.20-0.96) | 1.07(0.50-2.25) |
| PD-L1(+) | 83 vs 88 | 0.56(0.38-0.82) | 0.82(0.53-1.25) | 28 vs 30 | 0.42(0.21-0.82) | 0.50(0.25-1.02) |
| **TC/IC Combined (**≥**5% cutoff)** |  |  |  |  |  |  |
| PD-L1(-) | 101 vs 104 | 0.45(0.31-0.65) | 0.53(0.34-0.81) | 46 vs 32 | 0.41(0.22-0.75) | 0.85(0.46-1.57) |
| PD-L1(+) | 46 vs 50 | 0.65(0.40-1.07) | 0.89(0.51-1.53) | 15 vs 17 | 0.53(0.22-1.29) | 0.52(0.21-1.29) |

\*defined as [(# of PD-L1+ TC + # of PD-L1+ IC) /(total # of TC)] x100

**Supplementary Table 5. Associations of MET and/or PD-L1 expression on tumor cells with treatment outcomes:**

**(A) MET and/or TC PD-L1 expression analyzed as three groups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | N | No. of events | Median months  (95%CI) | Adjusted hazard ratio (95%CI)\* | Adjusted P\* |
| PFS |  |  |  |  |  |
| MET(-) and PD-L1(-) | 219 | 122 | 7.3(5.8-8.2) | reference |  |
| MET(+)PD-L1(-) or MET(-)PD-L1(+) | 131 | 85 | 5.4(3.7-5.6) | 1.28(0.96-1.72) | 0.097 |
| MET(+) and PD-L1(+) | 47 | 31 | 5.6(3.8-8.1) | 1.24(0.83-1.85) | 0.290 |
| OS | N |  |  |  |  |
| MET(-) and PD-L1(-) | 219 | 95 | 27.0(19.0-NR) | reference |  |
| MET(+)PD-L1(-) or MET(-)PD-L1(+) | 131 | 73 | 18.3(13.7- 26.0) | 1.29(0.94-1.76) | 0.115 |
| MET(+) and PD-L1(+) | 47 | 27 | 18.2(12.3- 23.5) | 1.55(1.01-2.38) | 0.047 |

**(B) MET and/or TC PD-L1 expression analyzed as two groups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | N | No. of events | Median months  (95%CI) | Adjusted hazard ratio (95%CI)\* | Adjusted P\* |
| PFS |  |  |  |  |  |
| MET(-) and PD-L1(-) | 219 | 122 | 7.3(5.8-8.2) | reference |  |
| MET(+) and/or PD-L1+ | 178 | 116 | 5.5(3.8-5.7) | 1.27(0.97-1.65) | 0.078 |
| OS |  |  |  |  |  |
| MET(-) and PD-L1(-) | 219 | 95 | 27.0(19.0-NR) | reference |  |
| MET(+) and/or PD-L1+ | 178 | 100 | 18.3(14.6-22.0) | 1.35(1.02-1.80) | 0.039 |

PFS: Progression free survival; OS: Overall survival

\*adjusted for treatment, IMDC risk group, presence of bone metastases and number of previous VEGFR TKI treatment (0, 1, or ≥2)

**Supplementary Table 6. Treatment comparison on PFS and OS, subgroup analysis by MET and PD-L1 (≥1% cutoff) expression on tumor cells**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **N** | **CABOZANTINIB (C)** | **N** | **EVEROLIMUS( E)/ SUNITINIB (S)** | **Hazard ratio**  **(C vs E/S)**  **(95%CI)** | **p-interaction** |
| **PFS** |  |  |  |  |  |  |
| MET (-) & TC PD-L1(-) | 114 | 9.2(7.3-13.8) | 105\* | 5.5(3.9-7.2) | 0.49(0.34-0.70) |  |
| MET (+) and/or TC PD-L1(+) | 86 | 7.4(5.6-9.0) | 92\*\* | 3.6(2.6-4.2) | 0.46(0.32-0.67) | 0.791 |
| **OS** |  |  |  |  |  |  |
| MET (-) & PD-L1(-) | 114 | 30.0(19.0-NR). | 105\* | 20.7(17.2-35.4) | 0.74(0.50-1.11) |  |
| MET (+) and/or TC PD-L1(+) | 86 | 26.4(18.1-35.0) | 92\*\* | 13.9(9.1-18.8) | 0.55(0.37-0.81) | 0.254 |

**\*** **EVEROLIMUS/SUNITINIB :** 86/19;

**\*\*** **EVEROLIMUS/ SUNITINIB:** 62/30;

**Supplementary Table 7. Association of immune cell density (ICD) tertile groups\* with PFS, OS, ORR and DCR**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **METEOR (N=301)** | | | **CABOSUN (N=110)** | | | **Total (N=411)** | | |
|  | **Total**  **N** | **No. of events** | **HR**  **(95%CI)\*\*** | **Total**  **N** | **No. of events** | **HR**  **(95%CI)\*\*** | **Total**  **N** | **No. of events** | **HR**  **(95%CI)\*\*** |
| **PFS** |  |  |  |  |  |  |  |  |  |
| Low ICD | 106 | 70 | 1(reference) | 31 | 20 | 1(reference) | 137 | 90 | 1(reference) |
| Intermediate ICD | 101 | 60 | 1.02(0.71-1.46) | 36 | 18 | 0.70(0.37-1.34) | 137 | 78 | 0.96(0.70-1.31) |
| High ICD | 94 | 53 | 0.97(0.67-1.39) | 43 | 27 | 0.85(0.45-1.59) | 137 | 80 | 0.94(0.69-1.28) |
| p-value\*\*\* |  |  | 0.958 |  |  | 0.560 |  |  | 0.919 |
| **OS** |  |  |  |  |  |  |  |  |  |
| Low ICD | 106 | 49 | 1(reference) | 31 | 16 | 1(reference) | 137 | 65 | 1(reference) |
| Intermediate ICD | 101 | 44 | 1.04(0.68-1.57) | 36 | 23 | 1.21(0.64-2.30) | 137 | 67 | 1.06(0.75-1.50) |
| High ICD | 94 | 48 | 1.26(0.84-1.88) | 43 | 23 | 1.08(0.56-2.06) | 137 | 71 | 1.19(0.84- 1.67) |
| p-value\*\*\* |  |  | 0.498 |  |  | 0.839 |  |  | 0.611 |
| **ORR** | **Total** | **ORR N** | **ORR**  **%** | **Total** | **ORR N** | **ORR**  **%** | **Total** | **ORR N** | **ORR**  **%** |
| Low ICD | 106 | 12 | 11% | 31 | 3 | 10% | 137 | 15 | 11% |
| Intermediate ICD | 101 | 13 | 13% | 36 | 4 | 11% | 137 | 17 | 12% |
| High ICD | 94 | 10 | 11% | 43 | 10 | 23% | 137 | 20 | 15% |
| p-value\*\*\* |  |  | 0.894 |  |  | 0.095 |  |  | 0.364 |
| **DCR** | **Total** | **DCR N** | **DCR**  **%** | **Total** | **DCR N** | **DCR**  **%** | **Total** | **DCR N** | **DCR**  **%** |
| Low ICD | 106 | 78 | 74% | 31 | 22 | 71% | 137 | 100 | 73% |
| Intermediate ICD | 101 | 77 | 76% | 36 | 23 | 64% | 137 | 100 | 73% |
| High ICD | 94 | 67 | 71% | 43 | 25 | 58% | 137 | 92 | 67% |
| p-value\*\*\* |  |  | 0.729 |  |  | 0.258 |  |  | 0.287 |

**\*** The cut off values were <650 for low ICD, 650-1437 for intermediate ICD and >1437 for high ICD based on the joint distribution of two studies.

**\*\*** adjusted for treatment, IMDC risk group, presence of bone metastases, number of previous VEGFR TKI treatment (1 or ≥2 for METEOR, 0, 1 or ≥2 for combined analyses**).**

\*\*\*Wald chi-square test from Cox regression was conducted for PFS and OS; Cochran-Armitage trend test was used to compare ORR and DCR among the tertile groups.

**Supplementary Table 8. Association of immune cell density (ICD) continuous scores with PFS and OS**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **METEOR (N=301)** | | **CABOSUN (N=110)** | | **Total (N=411)** | |
|  | **No. of events** | **HR**  **(95%CI)\*\*** | **No. of events** | **HR**  **(95%CI)\*\*** | **No. of events** | **HR**  **(95%CI)\*\*** |
| **PFS** |  |  |  |  |  |  |
| Continuous score\* | 183 | 1.04(0.76- 1.42) | 65 | 0.78(0.43-1.41) | 248 | 0.97(0.74-1.27) |
| p-value |  | 0.811 |  | 0.415 |  | 0.823 |
| **OS** |  |  |  |  |  |  |
| Continuous score\* | 141 | 1.34(0.91-1.98) | 62 | 1.03(0.56-1.91) | 203 | 1.24(0.89-1.72) |
| p-value |  | 0.142 |  | 0.924 |  | 0.197 |

\*Log10 transformed for continuous score.

**\*\*** adjusted for treatment, IMDC risk group, presence of bone metastases and number of previous VEGFR TKI treatment (1 or ≥2 for METEOR, 0, 1 or ≥2 for combined analyses**).**

**Supplementary Table 9. Treatment comparison on PFS and OS, subgroup analysis by immune cell density (ICD) (dichotomized at the upper 33% tertile value from the joint distribution of two trials)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **N** | **CABOZANTINIB (C)** | **N** | **EVEROLIMUS( E)/ SUNITINIB (S)** | **Hazard ratio**  **(C vs E/S)**  **(95%CI)** | **p-interaction** |
| **PFS** |  |  |  |  |  |  |
| **immune cell density** |  |  |  |  |  |  |
| Low | 135 | 8.3(6.6-9.4) | 139\* | 4.3(3.7-5.5) | 0.45(0.33- 0.61) |  |
| High | 73 | 7.4(5.6-11.0) | 64\*\* | 3.4(2.5-5.6) | 0.53(0.34-0.83) | 0.622 |
| **OS** |  |  |  |  |  |  |
| **immune cell density** |  |  |  |  |  |  |
| Low | 135 | 26.4(18.4-NR) | 139 | 19.0(17.1-22.4) | 0.74(0.52-1.04) |  |
| High | 73 | 26.6(17.3-NR) | 64 | 15.1(5.9-20.8) | 0.50(0.31-0.81) | 0.174 |

**\*** **EVEROLIMUS/SUNITINIB :** 113/26

**\*\*** **EVEROLIMUS/ SUNITINIB:** 41/23