## **SUPPLEMENTARY MATERIAL**

### **Plain language summary**

Checkpoint inhibitors (CPIs) are a group of anticancer drugs that are recommended as the first treatment for a type of kidney cancer that has spread to other parts of the body, called metastatic renal cell carcinoma (mRCC). Cabozantinib is a member of another group of anticancer drugs called tyrosine kinase inhibitors (TKIs), which are also approved for treating mRCC. Cabozantinib is approved for use after CPI treatment in the USA. We investigated how well either cabozantinib or other TKIs worked after CPI treatment when used for patients who were treated in routine clinical practice in the USA. We analyzed patient data from the US Oncology Network database supplemented by other medical records. We included data from 485 patients who had mRCC and had started TKI treatment (after CPI treatment) between May 2016 and November 2021. After 6 months of treatment with a TKI, 63% of patients who received cabozantinib had responded to treatment (based on their doctor’s assessment) compared with 46% of patients who received another TKI. We found that patients lived for a median of 19 months after starting treatment with either cabozantinib or another TKI. Overall, our study shows that cabozantinib is an effective treatment for mRCC for patients who have already received CPI treatment, based on how their disease responded to treatment.

### **Supplementary Table S1. Outcomes in the 2L TKI subgroup (2L cabozantinib and other 2L TKIs)**

|  |  |  |
| --- | --- | --- |
|  | **Unadjusted** | **Adjusted** |
| **2L cabo-zantinib** | **Other 2L TKIs** | **2L cabo-zantinib** | **Other 2L TKIs** |
| **RR-6m** |  |  |  |  |
| Patients with evaluable responses at 6 months | 78 | 28 | 103.9a | 63.6a |
| **RR-6m, n (%)**b | 44 (56.4) | 15 (53.6) | 57.9 (55.8) | 30.8 (48.4) |
| Rate difference (90% CI [non-inferiority]) | 2.8% (–14.8 to 20.5);*p*= 0.1159 | 7.4% (–5.6 to 20.3);*p* = 0.0137 |
| Rate difference (95% CI [superiority])c | NA | 7.4% (–8.2 to 22.9);*p* = 0.3528 |
| **ORR** |  |  |
| Patients with evaluable responses during full index period | 82 | 31 | 110.0a | 69.9a |
| **ORR, n (%)**b | 49 (59.8) | 18 (58.1) | 65.1 (59.2) | 36.9 (52.9) |
| Rate difference (90% CI [non-inferiority]) | 1.7% (–14.9 to 18.3);*p* = 0.1236 | 6.3% (–6.0 to 18.7);*p* = 0.0146 |
| Rate difference (95% CI [superiority])c | NA | 6.3% (–8.5 to 21.2);*p* = 0.4033 |
| **DOR** |  |  |
| Patients with complete or partial response in full index period | 49 | 18 | 65a | 37a |
| **DOR, months, median (95% CI)** | 9.4 (6.2–12.2) | 10.6(3.7–24.9) | 9.2(5.0–12.2) | 10.6(5.8–24.9) |
| Log-rank *p* value | 0.6904 | 0.3900 |
| **PFS** |  |  |
| n | 107 | 56 | 148a | 119a |
| **PFS, months, median (95% CI)** | 9.6(6.5–12.0) | 8.2(6.2–21.9) | 9.6(6.5–12.0) | 8.2(6.2–32.0) |
| Log-rank *p* value | 0.5855 | 0.3407 |
| **OS** |  |  |
| n | 107 | 56 | 148a | 119a |
| **OS, months, median (95% CI)** | 19.7(16.4–35.0) | 16.7(10.0–28.6) | 19.4(15.8–26.3) | 16.3(9.9–28.6) |
| Log-rank *p* value | 0.3503 | 0.5065 |

aCounts were weighted by IPTW; bProportion of the final study population with at least one complete or partial response; cWhen the lower bound CI exceeded the 10% non-inferiority margin (Δ=−10%), superiority testing was performed.

CI, confidence interval; DOR, duration of response; IPTW, inverse probability of treatment weighting; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RR-6m, response rate in the first 6 months of treatment; TKI, tyrosine kinase inhibitor.

### **Supplementary Table S2. Dose at initiation of index therapy**

| **Baseline dose** | **Cabozantinib****(n = 331)** | **Other TKIs****(n = 154)** |
| --- | --- | --- |
| **Cabozantinib, n (%)a** | Patients with available data | 330 | – |
| Recommended dose (60 mg/day) | 204 (61.6) | – |
| **Axitinib, n (%)b** | Patients with available data | – | 58 |
| Recommended dose (10 mg/day) | – | 41 (70.7) |
| **Lenvatinib, n (%)c** | Patients with available data | – | 25 |
| Recommended dose (18 mg/day) | – | 20 (80.0) |
| **Pazopanib, n (%)d** | Patients with available data | – | 49 |
| Recommended dose (800 mg/day) | – | 32 (65.3) |
| **Sunitinib, n (%)e** | Patients with available data | – | 22 |
| Recommended dose (50 mg/day) | – | 14 (63.6) |

a20 mg/day: n = 23 (6.9%); 30 mg/day: n = 1 (0.3%); 40 mg/day: n = 102 (30.8%); not documented: n = 1 (0.3%); bLow dose: n = 14 (24.1%); high dose: n = 2 (3.4%); not documented: n = 1 (1.7%); cLow dose: n = 5 (20.0%); dLow dose: n = 17 (34.7%); eLow dose: n = 8 (36.4%).

### **Supplementary Fig. S1. IPTW-adjusted duration of response**



CI, confidence interval; DOR, duration of response; HR, hazard ratio; IPTW, inverse probability of treatment weighting; mo, months; TKI, tyrosine kinase inhibitor.