Poster 45

# SAMETA: An open label, three-arm, multicenter Phase III study of savolitinib + durvalumab vs sunitinib and durvalumab monotherapy in patients with MET-driven, unresectable, locally advanced/metastatic papillary renal cell carcinoma (PRCC)

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## Objective

- SAMETA (NCT05043090) is a Phase III, open-label, randomized, controlled, multicenter study assessing the efficacy and safety of savolitinib in combination with durvalumab compared with sunitinib and durvalumab monotherapy in patients with MET-driven, unresectable and locally advanced or metastatic PRCC

## Summary


- Genomic abnormalities resulting in the dysregulation of MET signaling are common in cases of PRCC, providing a potential target in these MET-driven cases
- As the MET pathway may play a role in immunomodulation, data suggests combining MET inhibition (e.g., savolitinib) with a checkpoint inhibitor (e.g., durvalumab) may provide a synergistic anti-tumor effect
- Based on results from the SAVOIR and CALYPSO studies, the Phase III SAMETA study (NCT05043090) will analyze treatment with savolitinib and durvalumab in patients with MET-driven PRCC
- SAMETA is currently enrolling patients


## Plain language summary

### Why are we performing this research?

Kidney cancer is one of the top 10 most common cancers in the world. Clear cell renal cell carcinoma (ccRCC) is the most common type of kidney cancer. The second most common type of renal cell carcinoma, papillary renal cell carcinoma (PRCC), is associated with advanced disease and poor outcomes.

**Currently, there are no treatment options approved that specifically treat PRCC,** and patients are treated with drugs used for ccRCC, such as the drug sunitinib.

PRCC with abnormalities in a gene called MET is known as 'MET-driven PRCC'. This abnormality in the MET gene is a possible target for treatment.

Savolitinib is a drug that blocks mutated MET proteins, reducing the growth and spread of cancer. Studies have suggested that combining **savolitinib with durvalumab** (a drug that blocks the activity of a protein called programmed death ligand-1, making cancer cells more susceptible to being killed by immune cells) may have the **potential to be effective against "MET-driven PRCC."**

### How are we performing this research?

The SAMETA study will investigate patients with MET-driven PRCC. In the SAMETA study, participants will receive either:

- savolitinib with durvalumab
- sunitinib (current global standard treatment option)
- durvalumab on its own

**The study aims to see how effective the treatment is against MET-driven PRCC**, as well as any side effects to the treatments.

### Where can I access more information?

The SAMETA trial (NCT05043090) can be accessed at: https://clinicaltrials.gov/ct2/show/NCT05043090

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## Background

- Approximately 338,000 cancers of the kidney are diagnosed globally every year (2.4% of total cancer incidence)[1], with approximately 80% of these being renal cell carcinomas (RCCs)[2]
- Clear cell RCC (ccRCC) is the dominant histological subtype of RCC, accounting for approximately 75% of cases, and has steered the development of systemic therapies for all RCC subtypes[3–5]
- Papillary renal cell carcinoma (PRCC) is a form of non-clear cell RCC (nccRCC) and the second most common subtype of RCC, accounting for 10–15% of cases[5–7]
- PRCC is associated with poor clinical outcomes and a high incidence of metastasis. At present, there are no therapies approved specifically for PRCC[3,5,6]
- Many PRCC cases are MET-driven, a result of genomic abnormalities resulting in dysregulation of the MET signaling pathway, making these abnormalities a potential target for treatment[6,8]
  - In a Phase II study in patients with advanced PRCC (NCT02127710), approximately 40% of tumors were found to be MET-driven[9]

## Rationale

- Savolitinib is an oral, potent, and highly selective MET tyrosine kinase inhibitor (TKI) demonstrating preliminary clinical activity in advanced solid tumors[10–13]
- In the Phase III SAVOIR study (NCT03091192), savolitinib demonstrated encouraging antitumor activity compared with standard-of-care sunitinib in patients with MET-driven PRCC: progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) were all numerically greater with savolitinib vs sunitinib[14]
  - While sample size and follow-up were limited in SAVOIR due to premature termination of the study, median PFS was 7.0 months (95% confidence interval [CI] 2.8, not calculated [NC]) vs 5.6 months (95% CI 4.1, 6.9), respectively (hazard ratio [HR] = 0.71; 95% CI 0.37, 1.36; p = 0.31), median OS was NC (95% CI 11.9, NC) vs 13.2 months (95% CI 7.6, NC) (HR = 0.51; 95% CI 0.21, 1.17; p = 0.11) and ORR was 27% (95% CI 13.3, 45.5) vs 7% (95% CI 0.9, 24.3)[14]
- The MET pathway may also play a role in immunomodulation. Non-clinical and clinical data suggest a possible synergistic antitumor effect of MET inhibitors with an immune checkpoint inhibitor, such as durvalumab[15,16]
- Durvalumab is a selective, high-affinity human IgG1 monoclonal antibody that binds to programmed cell death ligand-1 (PD-L1) and blocks PD-L1 from binding with programmed cell death-1 (PD-1) and CD80[17,18]
- The Phase I / II CALYPSO study (NCT02819596) investigating savolitinib plus durvalumab, showed a notable efficacy signal in patients with MET-driven PRCC with an acceptable safety profile: ORR was 57%, median PFS was 10.5 months (95% CI 2.9, 15.7) and median OS was 27.4 months (95% CI 7.3, not reached)[16]
- Therefore, savolitinib plus durvalumab may provide clinical benefit in patients with MET-driven PRCC

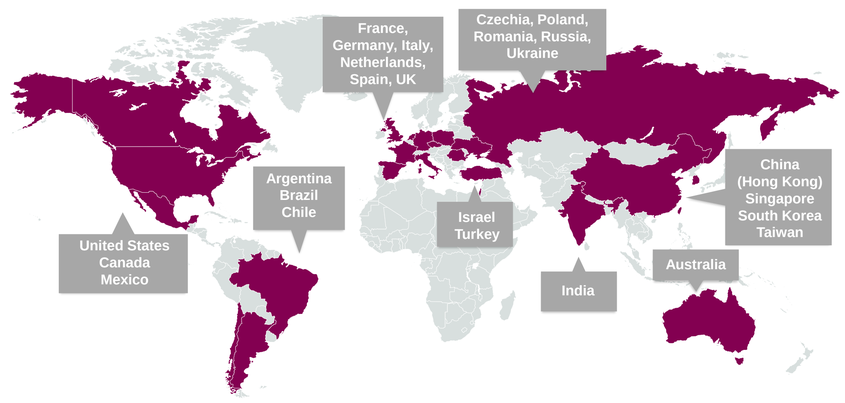
## SAMETA

- SAMETA is a Phase III, open-label, randomized, controlled, global, multicenter study assessing the efficacy and safety of savolitinib in combination with durvalumab vs sunitinib vs durvalumab monotherapy in patients with MET-driven, unresectable, and locally advanced or metastatic PRCC (**Table 1**)
- MET-driven PRCC is defined as detection of chromosome 7 gain, MET amplification, MET kinase domain variations, and / or hepatocyte growth factor (*HGF*) amplification (in the absence of co-occurring fumarate hydratase [*FH*] mutations) by central next-generation sequencing (NGS) testing[14]
- The study is recruiting across 25 countries at 165 centers globally, with an estimated 200 patients to be randomized (**Figure 1**)
- During biomarker pre-screening, approximately 28% of patients with PRCC who submitted a sample had eligible MET-driven status; of these, approximately 70% also met other eligibility criteria and were randomized

## Trial design

- Study design is shown in **Figure 2**
- Prior to randomization, participants will undergo a two-part screening process:
  - Part 1 screening involves prospective testing of tumor specimens to determine MET-driven status without co-occurring *FH* mutations and PD-L1 biomarker status. If a participant has confirmed MET-driven PRCC, they proceed to part 2 screening
  - Part 2 screening involves determining whether the participant meets the rest of the eligibility criteria
- Participants will be randomized in a 2:1:1 ratio into one of three treatment arms (A–C) with stratification by International Metastatic RCC Database Consortium risk group (favorable vs intermediate or poor) and PD-L1 expression tumor status (visually-estimated combined positive score ≥1% vs <1% / non-evaluable)
- Study treatment continues until Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) disease progression or another discontinuation criterion is met
- Participants will undergo imaging assessments (every 4 weeks ± 7 days for the first 54 weeks relative to randomization, then every 12 weeks ± 7 days relative to randomization) until RECIST 1.1-defined radiological progressive disease plus an additional follow-up scan

### Figure 1. Study location sites

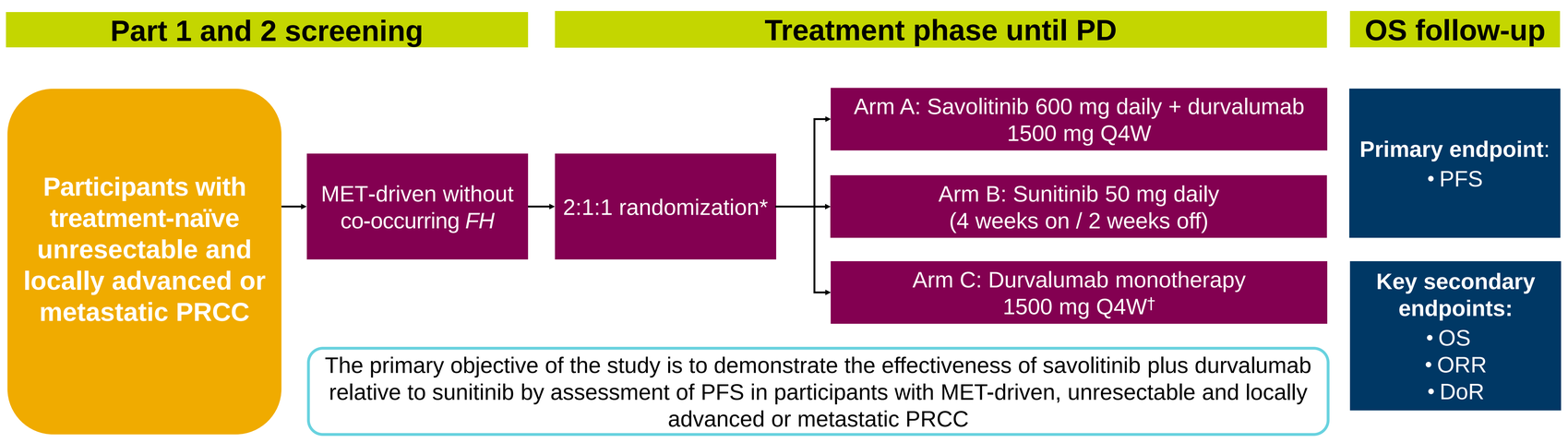



### Table 1. Key endpoints

| Endpoint | |
|---|---|
| **Primary** | **PFS**: defined as the time from randomization until progression per RECIST 1.1, as assessed by BICR, or death due to any cause |
| **Secondary** | **OS**: time from randomization until date of death due to any cause<br>**ORR**: proportion of participants who have a CR or PR as determined by BICR, per RECIST 1.1<br>**DoR**: time from the date of first documented response until date of documented progression as determined by BICR, per RECIST 1.1, or death due to any cause<br>**Pharmacokinetics**: plasma concentration of savolitinib and its metabolites pre- and post-dose |
| **Safety** | **Assessment of adverse events:** occurrence, frequency, relation to study intervention, NCI CTCAE grade, seriousness, death, and any leading to discontinuation of study intervention<br>**Vital signs, ECGs, and clinical safety laboratory assessments** including clinical chemistry, hematology, and urinalysis |

BICR, Blinded Independent Central Review; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DoR, duration of response; ECG, electrocardiogram; NCI, National Cancer Institute; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors 1.1

### Figure 2. SAMETA trial design




*The first patient was enrolled on October 28, 2021
†Participants randomized to the durvalumab monotherapy arm will be allowed to cross-over to the savolitinib plus durvalumab arm at the time of BICR-confirmed PD per RECIST 1.1 without any intervening systemic anti-cancer therapy following discontinuation of durvalumab monotherapy. Cross-over will not be allowed in any other case
BICR, blinded independent central review; DoR, duration of response; *FH*, fumarate hydratase; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRCC, papillary renal cell carcinoma; RECIST 1.1, Response Evaluation Criteria in Solid Tumors 1.1; Q4W, every 4 weeks

### Key inclusion criteria

- ≥18 years of age
- Histologically confirmed unresectable and locally advanced or metastatic PRCC
- PRCC must be centrally confirmed as MET-driven by a sponsor-designated, validated, NGS assay
- No prior systemic anti-cancer treatment in the metastatic setting; no prior exposure to MET inhibitors, durvalumab, or sunitinib in any setting

### Key exclusion criteria

- History of liver cirrhosis or other serious liver disease
- Spinal cord compression or brain metastases
- Active or prior cardiac disease or clinically significant ECG abnormalities
- Active infection (including COVID-19)
- Active interstitial lung disease / pneumonitis
- Active or prior documented autoimmune and inflammatory disorders
- Receipt of live attenuated vaccine within 30 days prior to the first dose of study intervention

## Statistical methods

- The full analysis set (FAS) will include all randomized participants according to treatment group assigned. Study population, demographics, efficacy, and health related quality of life data will be summarized and analyzed using the FAS. This analysis follows the principles of the intent-to-treat population
- Safety and pharmacokinetics data will not be formally analyzed, but will be summarized descriptively

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## Disclosures

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