39°CBU

SAMETA: An Open-Label, Three-arm, Multicentre 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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Introduction

- PRCC is a form of non-clear cell RCC (nccRCC) and the second most common subtype of RCC, accounting for 10–15% of cases[1-3]
- Many PRCC cases are MET-driven, characterised by genomic abnormalities resulting in dysregulation of the MET signalling pathway[2,4]
- Savolitinib is an oral, potent and highly selective MET tyrosine kinase inhibitor (TKI) demonstrating preliminary clinical activity in advanced solid tumours[5-8]
- In the Phase III SAVOIR study (NCT03091192), savolitinib demonstrated encouraging antitumour activity compared with standard-of-care sunitinib in patients with MET-driven PRCC[9]
- The MET pathway may also play a role in immunomodulation. Non-clinical and clinical data suggest a possible antitumour effect of MET inhibitors with an immune checkpoint inhibitor, such as durvalumab[10,11]
- 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[12,13]
- The Phase I / II CALYPSO study (NCT02819596) investigating savolitinib plus durvalumab, showed a notable efficacy signal in patients with MET-driven PRCC (n=17) with an acceptable safety profile: confirmed response rate was 53% (n=9; 95% confidence interval [CI] 28, 77), median PFS was 12.0 months (95% CI 2.9, 19.4) and median OS 27.4 months (95% CI 9.3, not reached)[11]
- Therefore, savolitinib plus durvalumab may provide clinical benefit in patients with MET-driven PRCC

Objectives

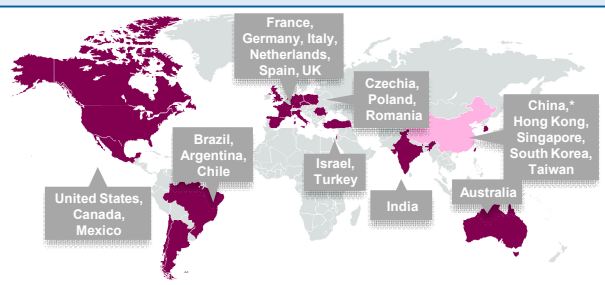
- SAMETA (NCT05043090) is a Phase III, open-label, randomised, controlled, multicentre study assessing the efficacy and safety of savolitinib in combination with durvalumab compared with sunitinib and durvalumab monotherapy in patients with MET-driven, unresectable and locally advanced or metastatic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

SAMETA

- SAMETA is a Phase III, open-label, randomised, controlled, global, multicentre study assessing the efficacy and safety of savolitinib in combination with durvalumab vs sunitinib monotherapy and 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 amplification (in the absence of co-occurring fumarate hydratase [FH] mutations) by central next-generation sequencing (NGS) testing[9]
- The study is recruiting across 23 countries at 165 centres globally, with an estimated 200 patients to be randomised (**Figure 1**)

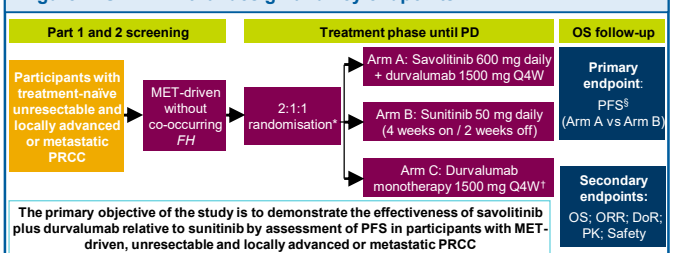
Figures

Figure 1. Study location sites*



*China will enrol for the combination arm, Arm A (savolitinib + durvalumab) only; patients enrolled from China will not contribute to global enrolment and will not be included in the primary analysis

Figure 2. SAMETA trial design and key endpoints



The primary objective of the study is to demonstrate the effectiveness of savolitinib plus durvalumab relative to sunitinib by assessment of PFS in participants with MET-driven, unresectable and locally advanced or metastatic PRCC

*The first patient was enrolled on 28 October 2021; †Participants randomised 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; §PFS assessed by BICR per RECIST 1.1

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; PK, pharmacokinetics; PRCC, papillary renal cell carcinoma; Q4W, every 4 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours 1.1

Table 1. Key endpoints

Primary	**PFS**: defined as the time from randomisation until progression per RECIST 1.1, as assessed by BICR, or death due to any cause
Secondary	**OS**: time from randomisation until date of death due to any cause
	ORR: proportion of participants who have a CR or PR as determined by BICR, per RECIST 1.1
	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
	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
	Vital signs, ECGs and clinical safety laboratory assessments including clinical chemistry, haematology 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 Tumours 1.1

Trial design

- Study design is shown in **Figure 2**
- Prior to randomisation, participants will undergo a two-part screening process:
  - Part 1 screening involves prospective testing of tumour specimens to determine MET-driven status without co-occurring FH mutations. PD-(L)1 biomarker status is not an eligibility criteria but will be used for stratification following enrolment. 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 randomised in a 2:1:1 ratio into one of three treatment arms (A–C) with stratification by International Metastatic RCC Database Consortium risk group (favourable vs intermediate or poor) and PD-L1 expression tumour status (visually-estimated combined positive score ≥1% / <1% / non-evaluable)
- Study treatment continues until objective disease progression per RECIST v1.1 or another discontinuation criterion is met
- Participants will undergo imaging assessments (every 6 weeks ± 7 days for the first 54 weeks relative to randomisation, then every 12 weeks ± 7 days relative to randomisation) until until progressive disease per RECIST v1.1, plus an additional follow-up scan

Statistical Analysis

- The full analysis set (FAS) will include all randomised participants according to treatment group assigned. Study population, demographics, efficacy and health related quality of life data will be summarised and analysed using the FAS. This analysis follows the principles of the intent-to-treat population
- Safety and pharmacokinetics data will not be formally analysed, but will be summarised descriptively; safety will be analysed in the safety analysis set (all randomised patients who received at least one dose of study drug)

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
- Participants with clear-cell components <50% permitted, provided the dominant histology is papillary

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 electrocardiogram (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

Summary

- Genomic abnormalities resulting in the dysregulation of MET signalling 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 an antitumour effect
- The Phase III SAMETA study (NCT05043090) will evaluate treatment with savolitinib and durvalumab in patients with MET-driven PRCC, based on encouraging data from the SAVOIR and CALYPSO studies
- SAMETA is currently enrolling patients

References

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