A PHASE 1/2, OPEN LABEL DOSE-ESCALATION AND EXPANSION TRIAL OF NKT2152, AN ORALLY ADMINISTERED HIF2α INHIBITOR, TO INVESTIGATE SAFETY, PK, PD AND CLINICAL ACTIVITY IN PATIENTS WITH ADVANCED ccRCC

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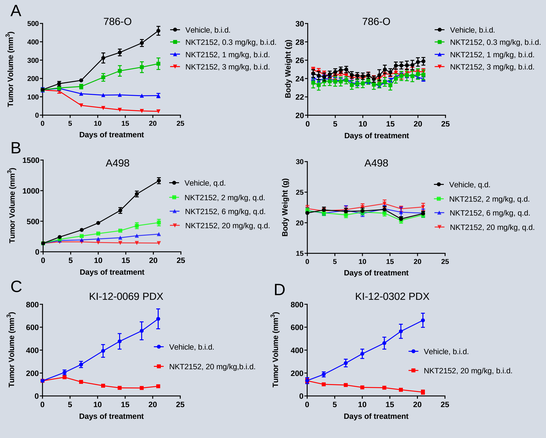
Abstract 49

Background

- Hypoxia-inducible factor-2α (HIF2α) is a pivotal oncogenic driver in clear cell renal cell carcinoma (ccRCC), which is characterized in most cases (~90%) by the inactivation of von Hippel-Lindau (VHL) tumor suppressor. VHL loss leads to HIF2α accumulation and constitutive activation of its downstream genes important in carcinogenesis.
- HIF2α represents an important therapeutic target in ccRCC and potentially other cancers.
- NKT2152 is a novel, potent, selective orally available HIF2α inhibitor optimized for enhanced PK exposure and sustained target inhibition which has demonstrated robust activity in both ccRCC cell line-derived and patient-derived xenograft RCC and other solid tumor models.
- This is a Phase 1/2 open label, multicenter, first-in-human study of NKT2152 in adults with advanced ccRCC (NCT05119335) (https://clinicaltrials.gov/ct2/show/NCT05119335)

NKT2152 Inhibits ccRCC Tumor Growth *In Vivo*



***In vivo* antitumor activity of NKT2152 in ccRCC models.** Daily NKT2152 treatment at indicated dose levels was initiated when the tumor reached 100 to 200 mm^3. All doses were well tolerated without significant body weight loss. (A) NKT2152 inhibited tumor growth in 786-O xenograft model. (B) NKT2152 inhibited tumor growth in A498 xenograft model. (C-D) NKT2152 inhibited tumor growth in patient-derived ccRCC xenograft models KI-12-0069 (C) and KI-12-0302 (D).

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OBJECTIVES

Primary

Phase 1

• To identify the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D) of NKT2152 in patients with relapsed or refractory ccRCC

Phase 2

• To evaluate the antitumor activity of NKT2152 by objective response rate (ORR) at the RP2D in patients with ccRCC

Secondary

• To evaluate the overall safety and tolerability of NKT2152 monotherapy
• To determine the pharmacokinetic (PK) profile of NKT2152 monotherapy
• To assess the pharmacodynamic (PD) effects of treatment with NKT2152
• To evaluate ORR of NKT2152 (Phase 1 only)
• To evaluate progression-free survival (PFS), durability of response and disease control rate of NKT2152

Exploratory

• To explore biomarkers considered potentially predictive of response to NKT2152

Patient Eligibility Criteria

KEY INCLUSION CRITERIA

- Age ≥ 18 yo
- Locally advanced or metastatic ccRCC not amenable to standard therapy (Phase 1) or progressed with at least 1 prior PD/L1 or VEGF targeting agent and ≤ 4 prior therapeutic regimens (Phase 2)
- Measurable disease per RECIST 1.1
- ECOG PS 0-2
- Adequate organ function
- Able to swallow oral medication

KEY EXCLUSION CRITERIA

- Known symptomatic brain metastases requiring >10mg/day of prednisone of equivalent.
- Pulse oximetry <92% , intermittent or chronic oxygen requirement
- Received prior HIF2α inhibitor
- History of other malignancy < 2 years ago.
- Significant cardiovascular disease.
- Bleeding diathesis or coagulopathy
- Major surgery within 4 weeks before first study drug administration.
- Active infection requiring systemic

Study Design

Adults with advanced ccRCC
- Phase 1 - not amenable to standard therapy
- Phase 2 - progressed on at least 1 prior VEGF and/or IO therapy (up to 4 lines of systemic therapy allowed)

• Neurologically stable CNS disease allowed
• 3+3 design with backfill expansion allowed per Safety Review Committee recommendation
• Response evaluation by RECIST v1.1

Phase 1 Dose Finding → Recommended Dose for Expansion → Phase 2 Dose Expansion

Endpoints

Primary:

Incidence of DLT events (Phase 1)
Investigator assessed ORR by RECIST v 1.1 (Phase2)

Secondary (Phase 1 and Phase 2)

Incidence of adverse events, PK, ORR (Phase1), DOR, DCR,TTR, PFS, OS

Assessments

Efficacy:
Radiographic assessments of the patient's tumor will be determined at defined intervals with response assessed using RECIST 1.1

Safety:
Safety will be assessed by periodic physical examinations, clinical laboratory assessments, and monitoring of AEs.

Dose-limiting toxicities and overall safety will be monitored by a safety committee comprised of the sponsor's medical monitor and all participating investigators, who will meet on a regular basis throughout the trial.

Pharmacokinetics:
The PK profile of NKT2152 will be assessed by determining plasma concentrations at intervals throughout the study.

Pharmacodynamics and Biomarkers:
The PD profile of NKT2152 and other markers that may be predictive of benefit of treatment will be analyzed.

Status

- Enrollment in study NKT2152-101(NCT05119335) is currently ongoing in the US.