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# EXPLORE-RCC: A phase II study of neoadjuvant zanzalintinib (ZANZA) plus nivolumab (NIVO) in patients with locally advanced and/or inoperable clear cell renal cell carcinoma (ccRCC)

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## Background

Patients (pts) with locally advanced ccRCC often have aggressive tumor biology, which can make complete surgical resection challenging. Such pts may benefit from neoadjuvant systemic therapy (tx) to shrink the primary tumor, improving resectability, facilitating organ preservation (partial from radical nephrectomy), or allowing a minimally invasive approach. We designed the EXPLORE-RCC trial to evaluate neoadjuvant ZANZA plus NIVO in pts with locally advanced ccRCC.

## Trial design

This is a multisite, phase 2, single arm, open-label trial run through the Hoosier Cancer Research Network. Main inclusion criteria are age ≥ 18 years, ECOG Performance Status of 0-1, histologically confirmed ccRCC, and locally advanced (cT3/4, N0-1) and/or deemed surgically inoperable per surgeon discretion. Suspected soft tissue metastasis with longest diameter < 10mm or distant lymph nodes < 15 mm in short axis (non-measurable per RECIST 1.1 criteria) are allowed. Main exclusion criteria are non-clear cell histology, measurable metastatic disease per RECIST 1.1 criteria, and prior systemic treatment for RCC. Enrolled subjects will receive 12 weeks (w) of ZANZA 100mg orally once daily plus NIVO intravenously per standard of care (SOC) dosing, followed by restaging scans and adaptive treatment pending surgical operability. Pts who (1) are deemed operable will undergo resection (Cohort A), (2) remain inoperable can receive up to 48w total of ZANZA plus NIVO (Cohort B1) with option to resect when operability is feasible, or (3) have progression of disease will stop protocol mandated tx to receive SOC tx (Cohort B2). The primary endpoint is overall response rate (ORR) after 12w of tx. The study has 80% power to detect an ORR improvement from a historical of 0.3 to 0.45 with a 0.05 one-sided type I error and an estimated 10% drop out rate (n=69). Key secondary/exploratory endpoints include conversion from inoperable to operable, safety, disease free survival, overall survival, surgery-related outcomes/complications including Clavien-Dindo, pathologic complete response, and biomarker correlatives. The trial is active (ClinicalTrials.gov NCT06794229).

## Clinical trial identification

NCT06794229.

## Legal entity responsible for the study

Hoosier Cancer Research Network.

## Funding

Exelixis.

## Disclosure

Q. Qin: Financial Interests, Personal, Advisory Board: Exelixis, Janssen, Eisai; Financial Interests, Institutional, Research Funding: Exelixis, Janssen; Financial Interests, Personal, Invited Speaker: Dava Oncology, Mashup Media, MJH Life Sciences. H. Hammers: Financial Interests, Personal, Other, Honoraria: Bristol-Myers Squibb; Financial Interests, Personal, Advisory Role: Bristol-Myers Squibb, Pfizer, Exelixis, Bayer, Novartis, Merck, ARMO BioSciences, Corvus Pharmaceuticals, Surface Oncology; Financial Interests, Institutional, Research Funding: Bristol-Myers Squibb, Merck, Surface Oncology, NGM Biopharmaceuticals, Aveo, Hibercell, NiKang Therapeutics, Exelixis, Werewolf Therapeutics; Financial Interests, Personal, Other, travel/accomodations/expenses: Bristol-Myers Squibb, Merck, Pfizer, Lilly, Novartis. J. Vento: Financial

Interests, Personal, Invited Speaker: MJH Life Sciences. K. Courtney: Financial Interests, Institutional, Local PI: Astellas, Clovis Oncology, Exelixis, Amgen, Harpoon, Pfizer, Novartis, Surface Oncology, Myovant Sciences, Celgene, AstraZeneca, Janssen, DualityBio, Stemline Therapeutics. D.M. Geynisman: Financial Interests, Personal, Advisory Board: Merck, Exelixis; Financial Interests, Personal, Advisory Role: Axiom Healthcare Strategies, Clearview, Exelixis; Financial Interests, Personal, Invited Speaker: Curio Science, Targeted Oncology; Financial Interests, Institutional, Research Funding: Regeneron Pharmaceuticals, Merck, Bristol Myers Squibb. M.A. Reimers: Financial Interests, Personal, Advisory Board, 5SEP2024, 29NOV2023: Lilly; Financial Interests, Personal, Advisory Board: Pathos AI Inc; Financial Interests, Personal, Advisory Board, 31MAY2024: Astellas; Financial Interests, Personal, Advisory Board, 15FEB2025: Eisai; Financial Interests, Institutional, Local PI: BMS, Merck, Crisper Therapeutics, Pathos AI Inc, Lilly. T. Zhang: Financial Interests, Personal, Advisory Board: Merck, Exelixis, Sanofi-Aventis, Janssen, AstraZeneca, Pfizer, Amgen, BMS, Eisai, Aveo, Bayer, Eli Lilly, Gilead, Novartis, EMD Serono, Xencor, Dendreon; Financial Interests, Personal, Other, Consulting: MJH Associates, Vanaiam, Aptitude Health, PeerView, Clinical Care Options; Financial Interests, Institutional, Steering Committee Member: Merck; Financial Interests, Institutional, Coordinating PI: Janssen, Exelixis; Financial Interests, Institutional, Local PI: AstraZeneca, Pfizer, Astellas, Eli Lilly, Tempus, ALX Oncology, Janux Therapeutics, OncoC4, Bayer; Non-Financial Interests, Advisory Role, Medical Steering Committee: Kidney Cancer Association; Non-Financial Interests, Advisory Role, Scientific Advisory Board: KCCure; Non-Financial Interests, Advisory Role: Myrovlytis Trust; Non-Financial Interests, Member: ASCO, AACR. All other authors have declared no conflicts of interest.

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