Clinical trial summary (S2419)

Adding biotherapy or placebo to standard treatment for advanced kidney cancer (BioFront Trial)

What is the purpose of this clinical trial?

This trial asks if adding a specific type of **biotherapy**, or probiotic, to the usual treatment for a type of advanced kidney cancer can help the usual treatment work better.

The usual treatment includes **immunotherapy**, which helps the immune system fight cancer. Biotherapy uses material from living organisms. The biotherapy in this study is a pill that contains a type of "good" bacteria.

The study will compare 2 treatment approaches:

usual treatment + biotherapy	**vs.**	**usual treatment + placebo** A placebo is something that looks like the study drug but doesn't contain any medicine

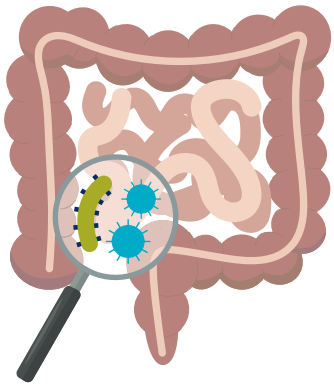
This trial is set up to find out:

- If adding biotherapy to the usual treatment for advanced kidney cancer can help the usual treatment work better
- If adding biotherapy to the usual treatment can help people with advanced kidney cancer live longer
- What side effects combining biotherapy with the usual treatment can cause

Why is this trial important?

The gut microbiome is the collection of bacteria and other microscopic organisms that live in the human digestive system (gut). Studies have shown that the gut microbiome probably affects how well immunotherapy works.

This study looks at a biotherapy treatment that causes changes in the gut microbiome. It will help researchers learn if this treatment can help immunotherapy work better for people with advanced kidney cancer. The study could lead to new and better treatment options for people in the future.



Who can be in this trial?

This trial is for adults, age 18 and older, with a type of kidney cancer called clear cell renal cell carcinoma.

This trial is for people who:

- Have advanced cancer (cancer that's spread outside the kidneys or can't be treated with surgery or radiation alone)

This trial is not for people who:

- Are taking over-the-counter probiotic supplements
- Already received systemic therapy (like immunotherapy or targeted therapy) for advanced kidney cancer
- Are pregnant or breastfeeding

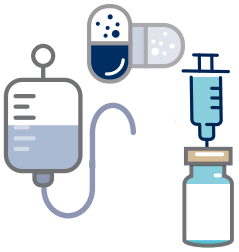
What treatments will I get?

A computer will randomly assign you to one of 2 study groups. Your doctor won't have control over which group you're assigned to. And you and your doctor won't know which group you're in until the study ends. This helps make sure the study results are fair and reliable.

You'll get:

- **The usual treatment for advanced kidney cancer: This could be one of several combinations of drugs**
- **Either biotherapy (a pill called MO-03) or a placebo pill**





You and your doctor will decide which usual combination of drugs is right for you:

- Every combination includes at least 1 immunotherapy drug.
- Some combinations also include a tyrosine kinase inhibitor (TKI). TKIs help stop cancer cells from growing.
- Some of the drugs are pills, and others are given through an IV (a needle placed in a vein in your arm) or as an injection (shot).

All of the usual combinations of drugs are approved by the FDA for treating kidney cancer. MO-03 is not approved by the FDA.

How long will I be in the trial?

You'll get treatment for up to 3 years, and you'll be in the study for up to 5 years total. After you stop treatment, you'll continue to have visits with your study doctor so they can see how you're feeling and if the cancer has gotten worse or come back.

Are there costs? Will I get paid?

The MO-03 and placebo are provided free in the study. To learn more about what costs will and won't be covered, talk to your health care provider and insurance provider.

You will not be paid for joining the study.

Where can I find more information about this trial?

- Talk with your health care provider
- Call the National Cancer Institute at **1-800-4-CANCER**
- Go to **www.ClinicalTrials.gov** and search the national clinical trial number: **NCT07383441**
- For a list of trial locations, visit **swog.org/NCI-S2419**

Key information

Protocol number: S2419

NCT number: NCT07383441

Trial sponsor: SWOG Cancer Research Network

Publishing date: April 2, 2026

Full trial title: Phase III Double Blinded Trial of Immune-based Therapy with a Live **Bio**therapeutic MO-03 or Placebo for **Front**line Therapy of Advanced Clear Cell Renal Cell Carcinoma (BioFront Trial)

Thank you!

When you join a clinical trial,
you're moving cancer medicine and patient care forward.

Welcome to the S2419 (BioFront) Kick Off Meeting

We are looking forward to your active participation and feedback.

- **There will be time at the end of the meeting for open forum discussion and Q&A.**

Hybrid Meeting Logistics:

- When asking questions or contributing to the discussion:
  - **In-person participants**: **Please use the in-room microphones (ensure that the microphone is turned on), so that your question/contribution can be heard by all in-person and online participants.**
  - **Online participants**:
    - During the presentation: Please place any questions in the **chat box**.
    - During open forum discussion: Please "**raise your hand**" and then un-mute yourself when called upon to contribute to the discussion. **If you are not speaking, please mute your line.**
- **This meeting is being recorded.**
  - The meeting slide set and recording will be posted via the SWOG.org website and CTSU CLASS learning management system (as a resource link under the current S2419 Require Site Initiation Training course).
- Meeting attendance is optional. We will not be providing certificates of attendance.



The meeting will begin at 4:15 PM CT.

Agenda

4:15–4:18 PM • **Introduction and Welcome** – Pedro C. Barata, MD MSc

4:18–4:30 PM • **S2419 Background, Overview & Key considerations** – Pedro C. Barata, MD MSc

4:30–4:38 PM • **Specimen Collection for Future Correlative Studies** – Nazli Dizman, MD

4:38–4:45 PM • **S2419 Resources, FAQs and Current Status** – Pedro C. Barata, MD MSc

4:45–4:53 PM • **Patient Advocate Perspective** – Laura Esfeller

4:53–5:12 PM • **Q & A and Open Forum Discussion – All Meeting Participants**
  - Moderator: Pedro C. Barata, MD MSc
  - Q & A Panel: Ulka Vaishampayan, MD, Sumanta K Pal, MD, Nazli Dizman, MD, Melissa Plets, MS, Laura Esfeller, Megan Keim

5:12–5:15 PM • **Wrap-up** – Pedro C. Barata, MD MSc

S2419

Phase III Double Blinded Trial of Immune-Based Therapy with a Live **Bio**therapeutic MO-03 or Placebo for **Front**line Therapy of Advanced Clear Cell Renal Cell Carcinoma [BioFront Trial]

NCT07383441

Study Chairs:
Pedro C. Barata, MD MSc
Ulka Vaishampayan, MD
Sumanta K Pal, MD

Champions:
ECOG-ACRIN - Shahid Ahmed, MD
Alliance - Elshad Hasanov, MD, PhD

Translational Medicine Chairs:
David J. McConkey, PhD
Nazli Dizman, MD

Co-Chair for Community Engagement:
Helen Moon, MD

Patient Advocate:
Laura Esfeller

Statisticians:
Cathy Tangen, DrPH
Melissa Plets, MS

Data Coordinators:
Michele Counts
Tonya Johnson

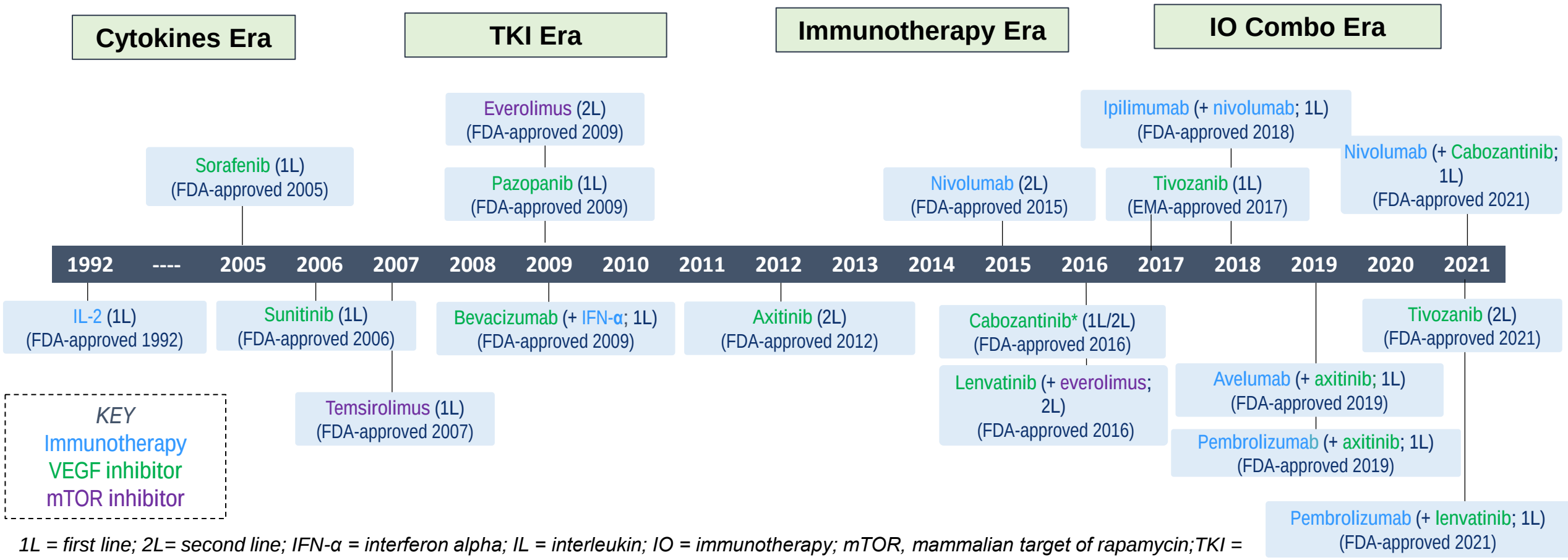
Protocol Project Manager:
Megan Keim

SWOG CANCER RESEARCH NETWORK

S2419 is being conducted under SWOG IND# 31836 for Blinded Drug MO-03 or placebo (NSC-854485).

NCI National Clinical Trials Network | NCI Community Oncology Research Program

Evolution of Systemic Therapy in Metastatic RCC



1L = first line; 2L= second line; IFN-α = interferon alpha; IL = interleukin; IO = immunotherapy; mTOR, mammalian target of rapamycin;TKI = tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR-2 = VEGF receptor-2

*Cabozantinib inhibits VEGFR-2, but also c-MET and AXL.22.

Dizman N, et al. *Nature Reviews Nephrol.* 2020;16:435–451.

Food and Drug Administration. Drug Approvals and Databases. https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases.

How do we improve on contemporary Immune therapy outcomes in advanced RCC?

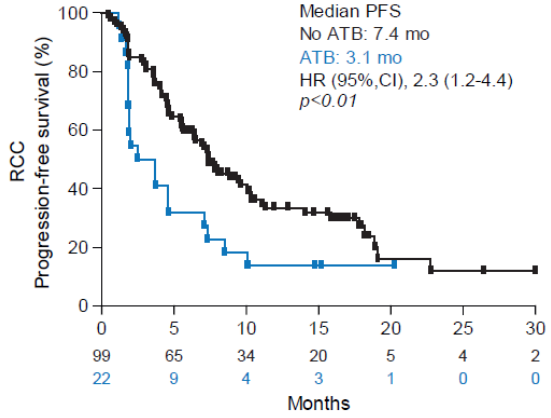
Microbiome!

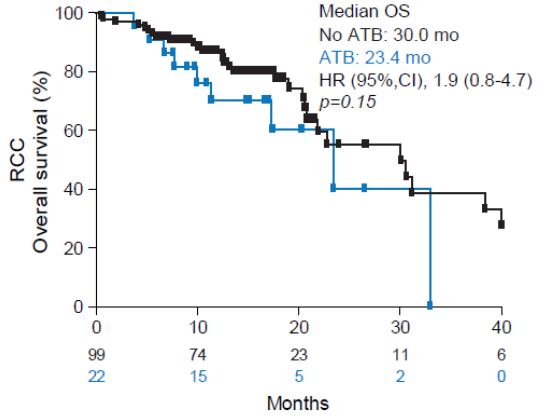
Microbiome in Renal Cell Carcinoma

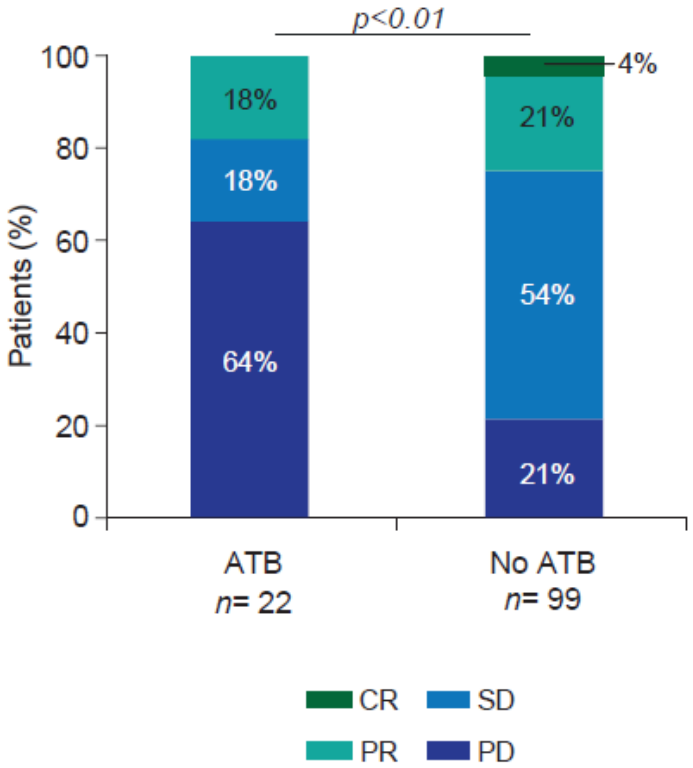
Antibiotic use associated with inferior outcomes

Summary:

- **121 pts with RCC**
- **239 pts with NSCLC**
- **Antibiotic use associated with inferior outcome in pts receiving checkpoint inhibitors**
- **Similar trends in NSCLC and RCC pts**







Treatment-*n* (%)				
	α-PD-(L)1 mAb	106 (88)	14 (88)	92 (88)
	α-PD-(L)1 mAb + α-CTLA-4	10 (8)	1 (6)	9 (8)
	α-PD-(L)1 mAb + Bev	5 (4)	1 (6)	4 (4)

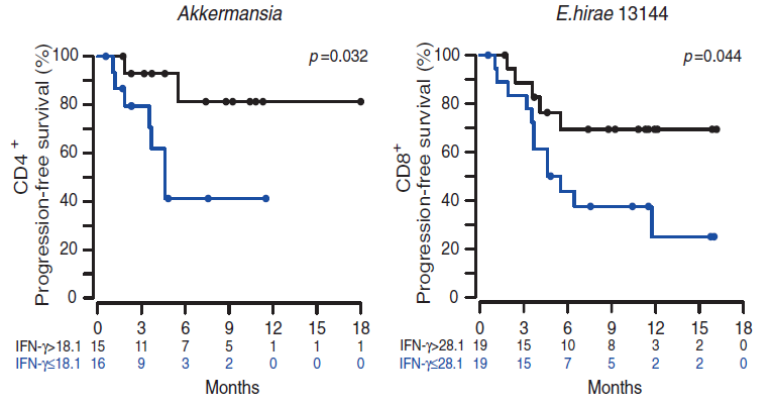
Derosa L *et al* Ann Oncol 2018 (RCC Investigators: DeRosa, Albiges, Escudier)

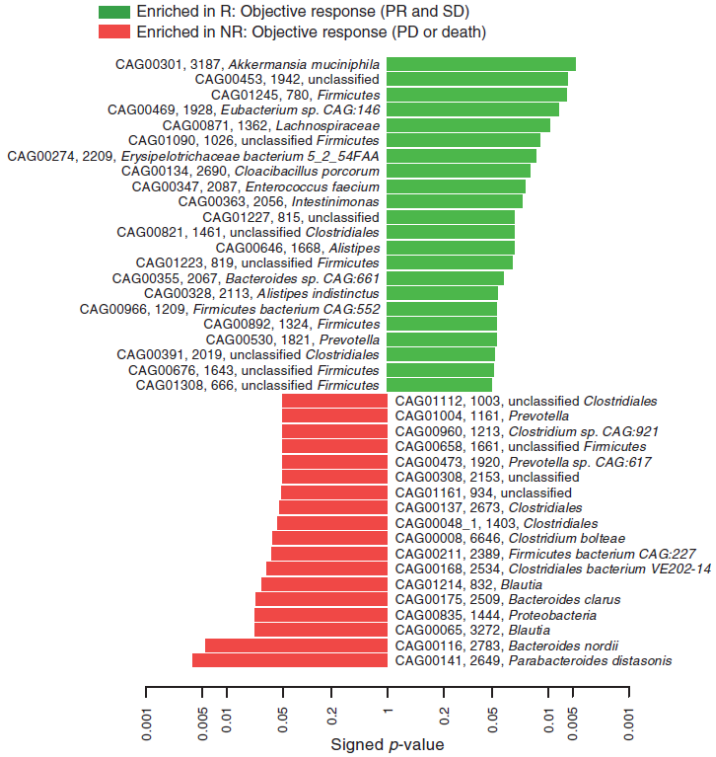
Microbiome in Renal Cell Carcinoma

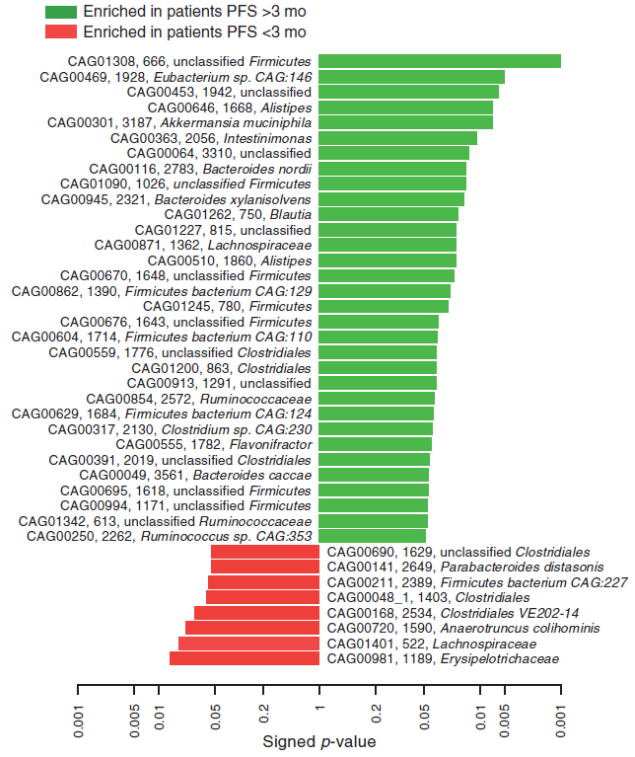
Specific bacterial species associated with response

Summary:

- **60 pts with NSCLC**
- **40 pts with RCC**
- **Baseline and serial stool collections after checkpoint inhibitor initiated**
- **Specific bacterial species associated with response**





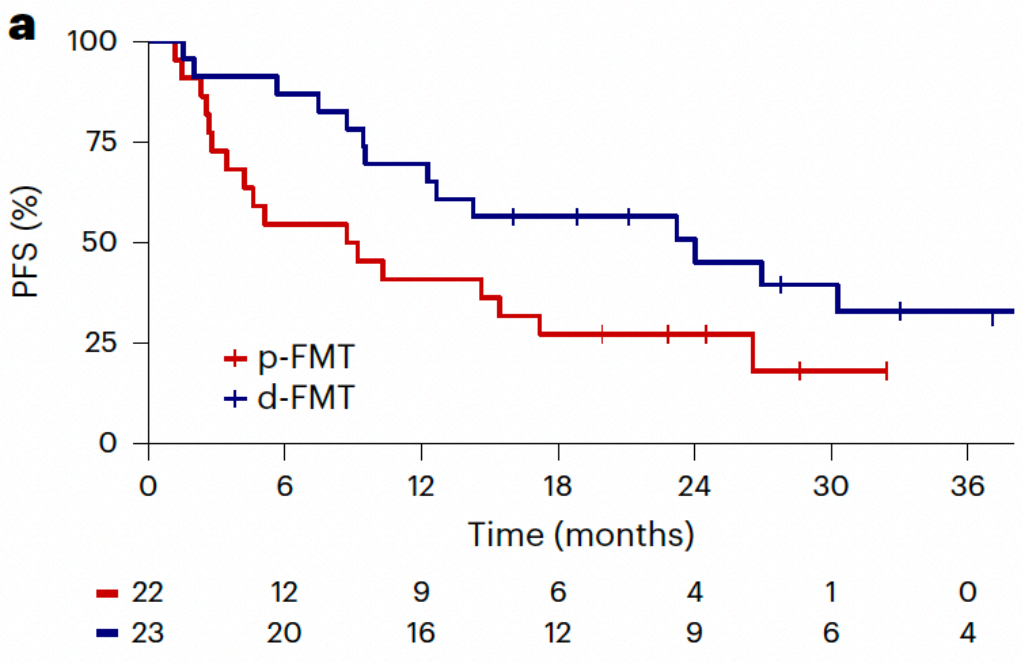


Routy B et al Science 2017 (RCC Investigators: DeRosa, Albiges, Escudier)

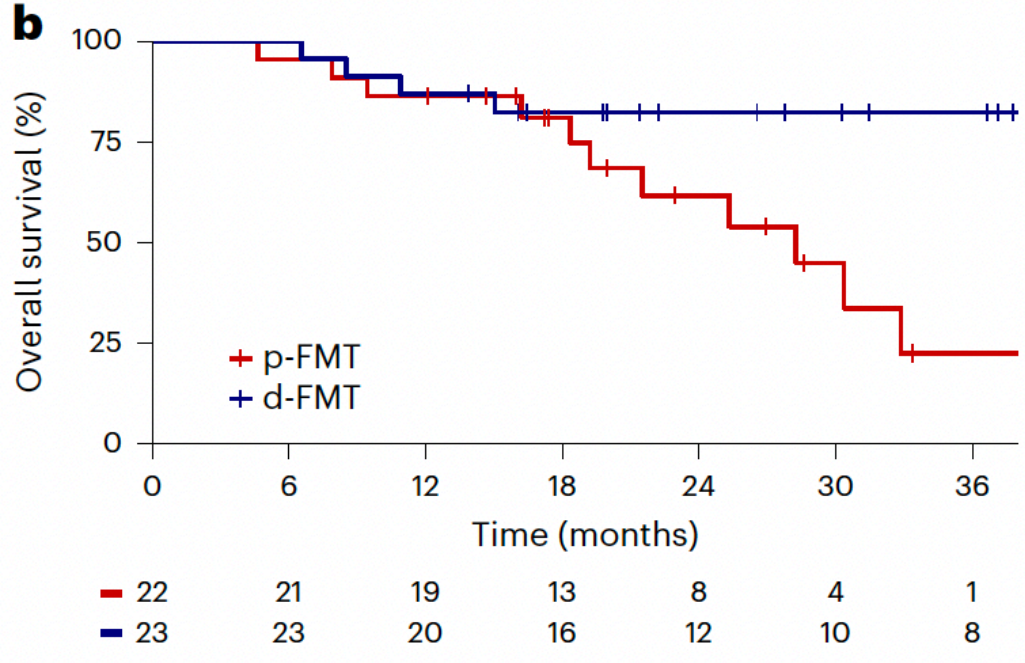
TACITO Trial

- Fecal microbiota transplantation (FMT) from complete ICI responders
- ORR = 52% vs 32%

24.0 vs 9.0 months
HR = 0.50, 90% CI: 0.27–0.92, *P* = 0.035

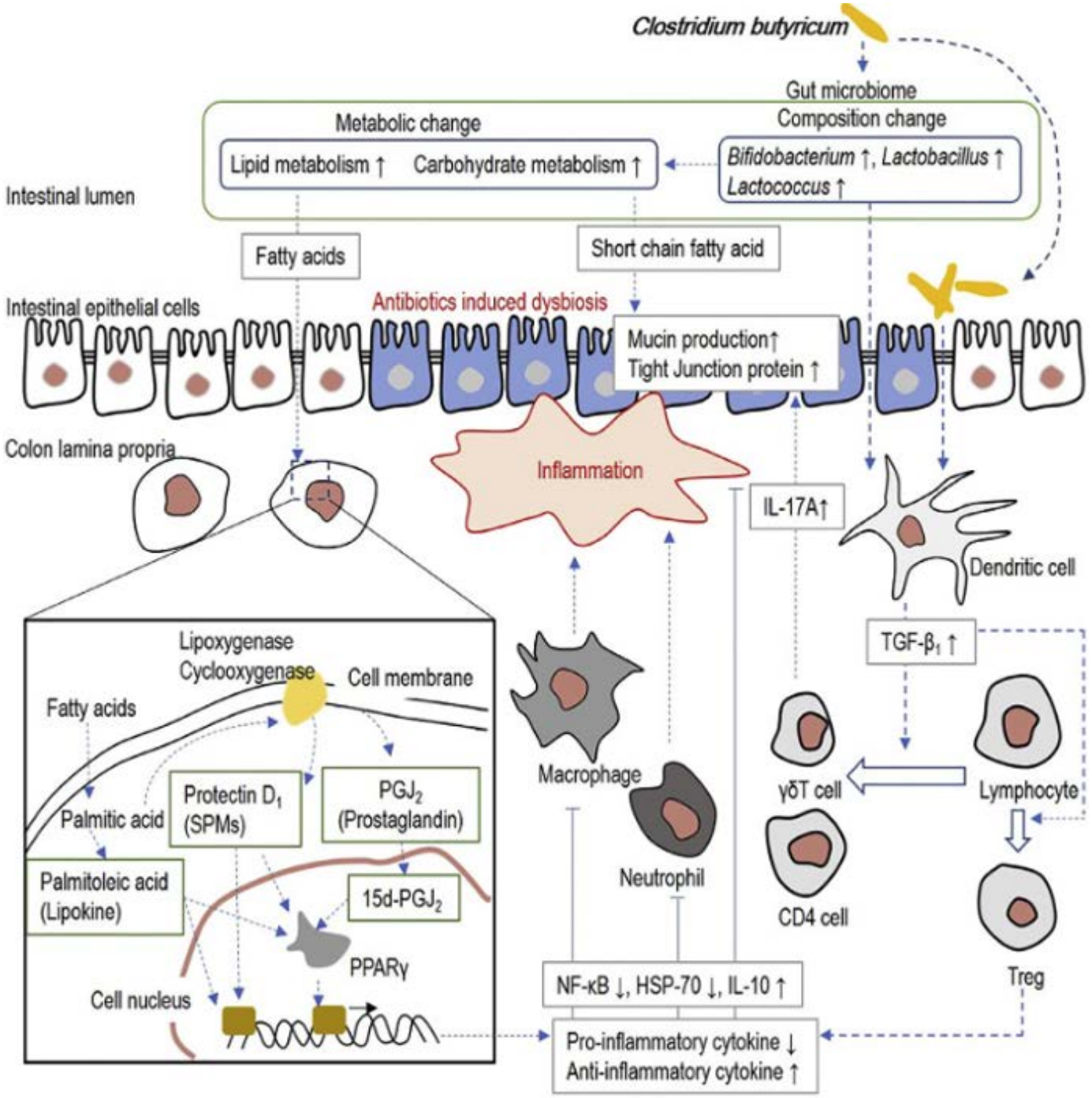


41.0 vs 28.3 months
HR = 0.36 (95% CI: 0.13–0.99), P = 0.167



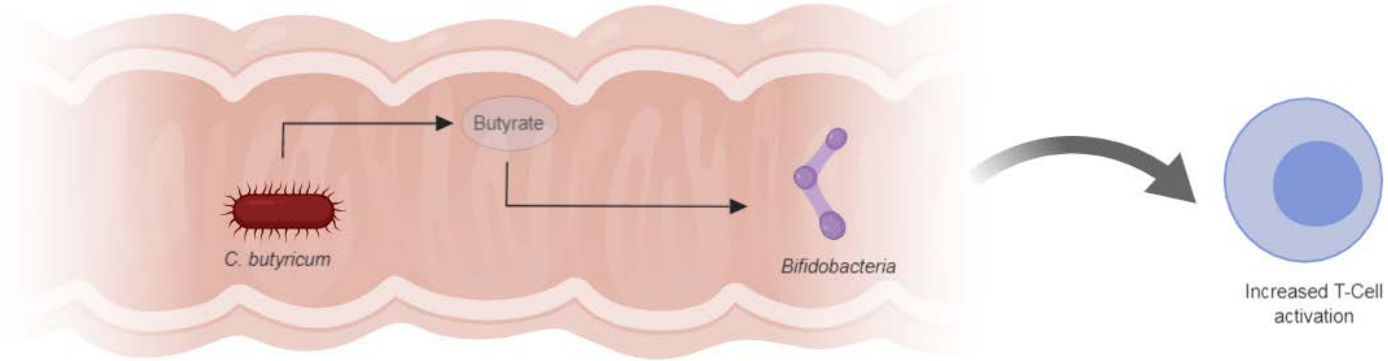
CBM588: Background and MOA

- CBM588 is an orally available live bacterial product containing a specific strain of *Clostridium butyricum*
- Proliferation in the lower gut is followed by production and release of butyrate
- Compositional changes in the gut flora ensue, with ↑ in *Bifidobacterium, Lactobacillus* and "favorable" species
- Complex effects on immune milieu are observed



Hagihara *et al.* iScience 2020

Microbiome in Renal Cell Carcinoma



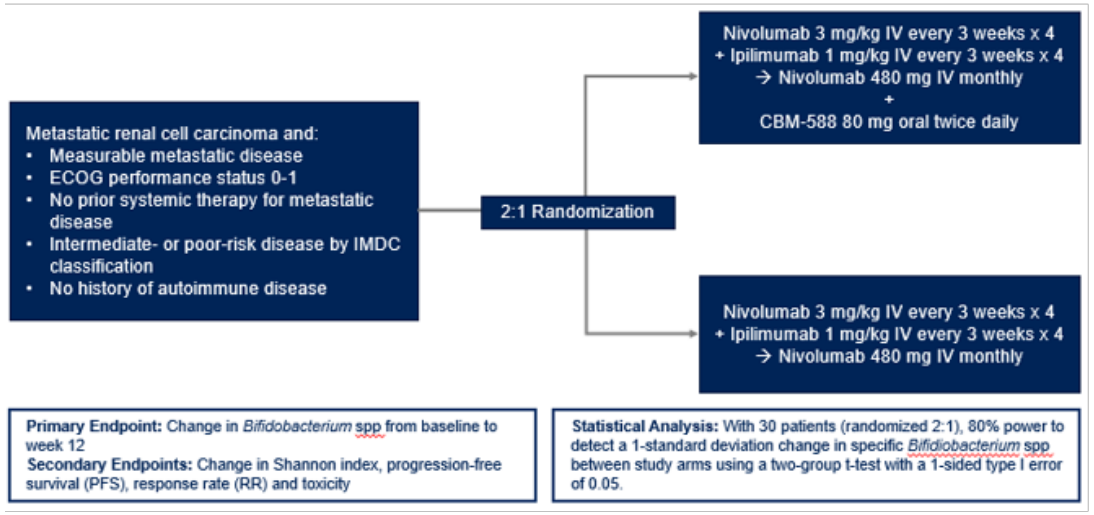
CBM588

- Live Biotherapeutic Product (LBP) containing *Clostridium butyricum* (*C. butyricum*) CBM588 strain
- *C. butyricum* produces short chain fatty acids, particularly butyric acid, and modulates the composition of the gastrointestinal (GI) microflora
- Miyarisan Pharmaceuticals (Tokyo, Japan) manufactures CBM588 for Osel, Inc.

- CBM588 capsules (MO) are a new formulation able to deliver higher doses with similar tolerability

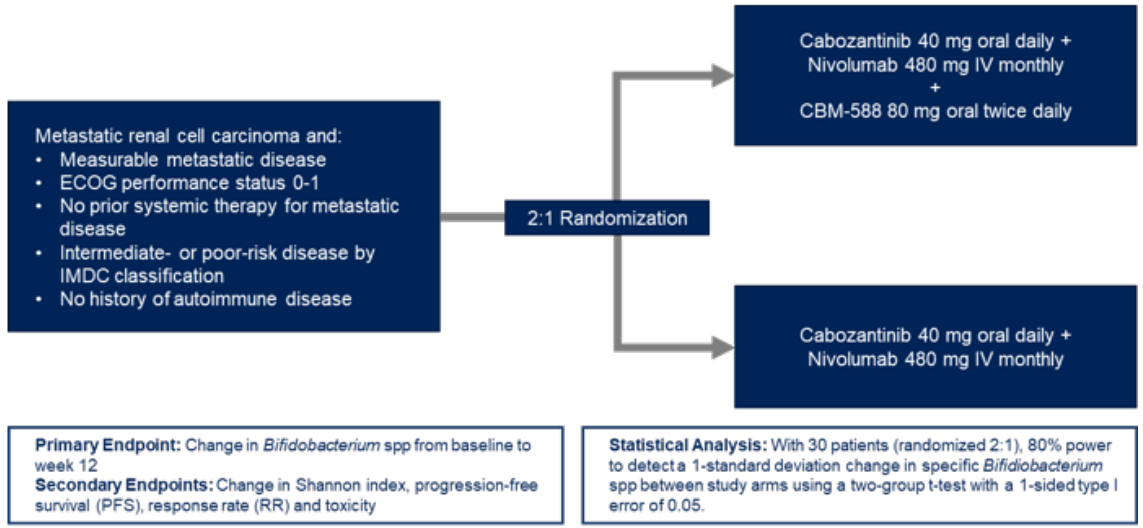
Phase I Studies Assessing CBM588

Nivolumab/Ipilimumab +/- CBM588



Dizman *et al* Nature Medicine 2022

Cabozantinib/Nivolumab +/- CBM588

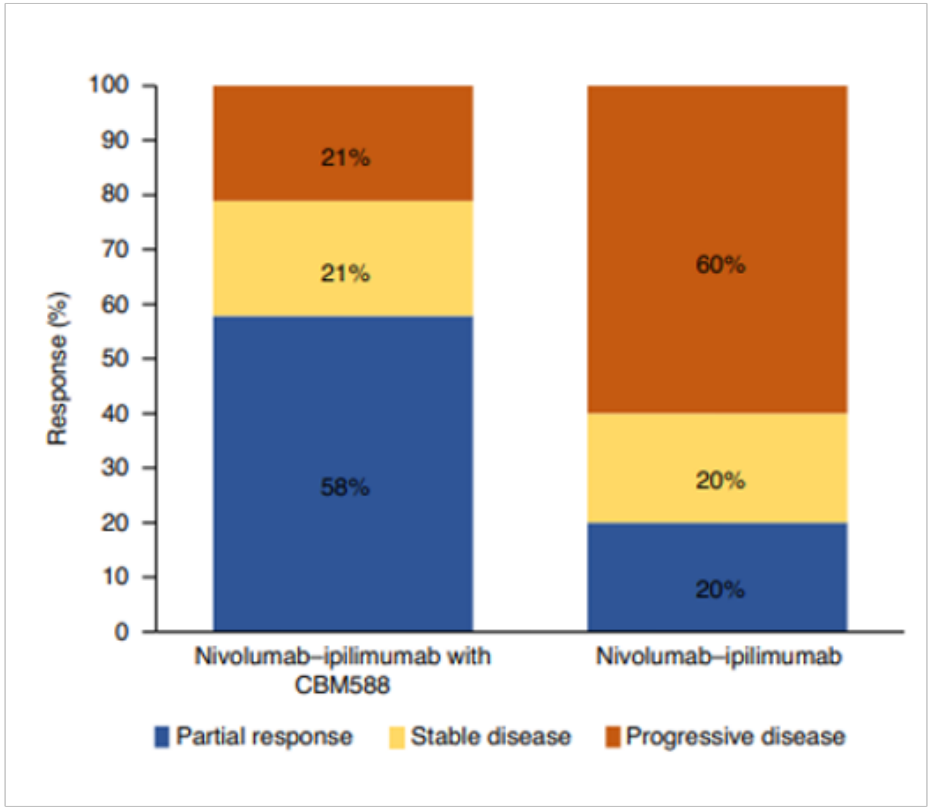


Ebrahimi *et al* Nature Medicine 2024

Dizman, Meza, Bergerot *et al.* Nature Medicine 2022

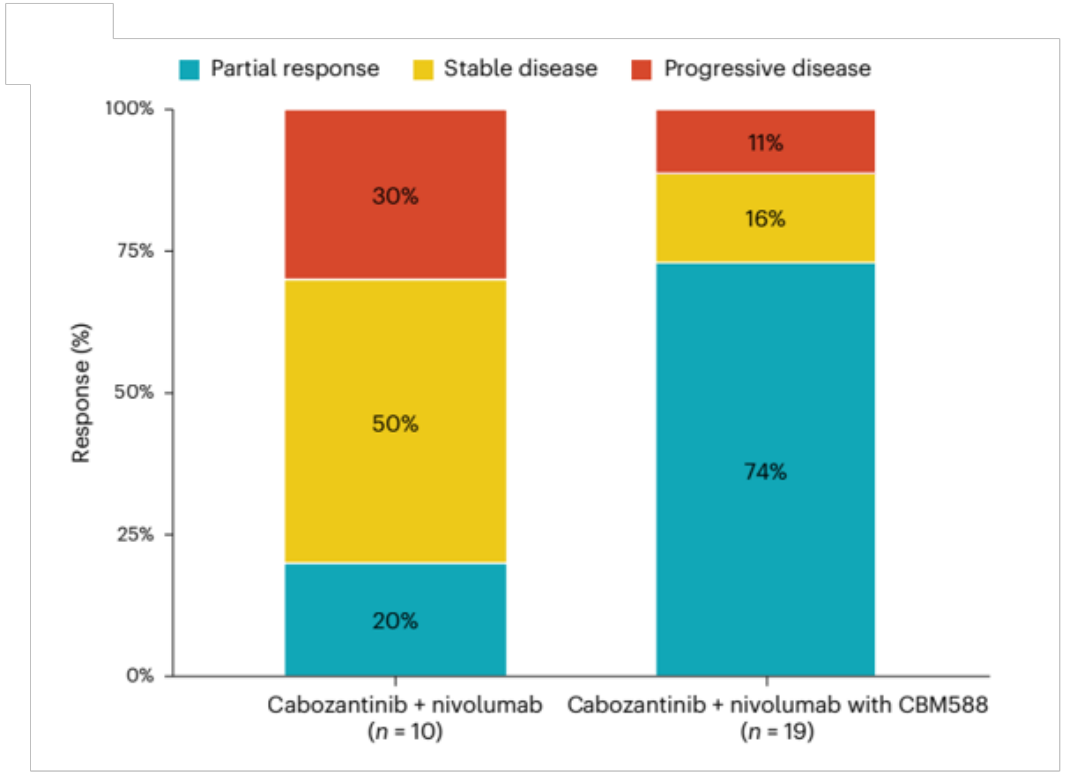
Phase I Studies Assessing CBM588: Response Rate (Separate)

Nivolumab/Ipilimumab +/- CBM588



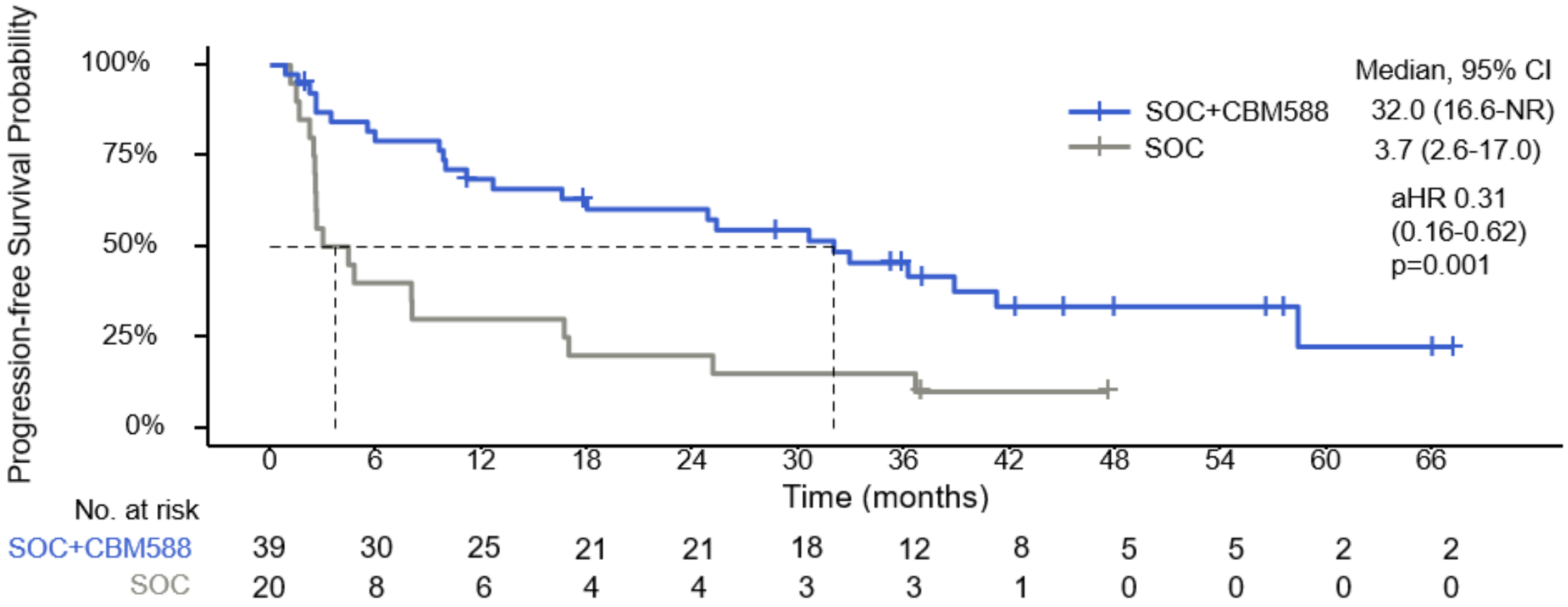
Dizman *et al* Nature Medicine 2022

Cabozantinib/Nivolumab +/- CBM588



Ebrahimi *et al* Nature Medicine 2024

Phase I Studies Assessing CBM588: PFS (Combined)



Winayak *et al* ASCO 2026

Phase I Studies Assessing CBM588: Dose Escalation

Nivolumab/Ipilimumab + CBM588

Metastatic renal cell carcinoma and:
- Measurable metastatic disease
- ECOG performance status 0-1
- No prior systemic therapy for metastatic disease
- Intermediate- or poor-risk disease by IMDC classification
- No history of autoimmune disease

Nivolumab/Ipilimumab + CBM588 DL1

Nivolumab/Ipilimumab + CBM588 DL2

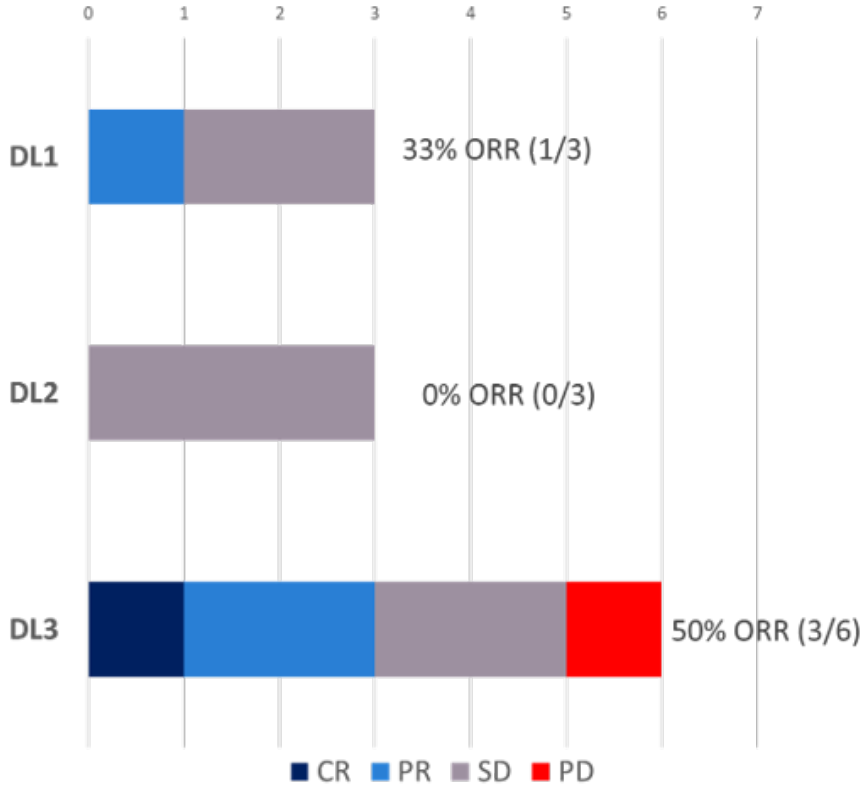
Nivolumab/Ipilimumab + CBM588 DL3

Primary Endpoint: Safety of novel CBM588 formulation
Secondary Endpoints: Change in Shannon index, progression-free survival (PFS), response rate (RR) and toxicity

Statistical Analysis: Classical 3+3 design

PI: Alexander Chehrazi-Raffle, MD

Response Rate in Dose Escalation



Zugman *et al* ASCO GU 2026

Phase I Studies Assessing CBM588: Dose Escalation

Nivolumab/Ipilimumab + CBM588

Metastatic renal cell carcinoma and:
- Measurable metastatic disease
- ECOG performance status 0-1
- No prior systemic therapy for metastatic disease
- Intermediate- or poor-risk disease by IMDC classification
- No history of autoimmune disease

Nivolumab/Ipilimumab + CBM588 DL1

Nivolumab/Ipilimumab + CBM588 DL2

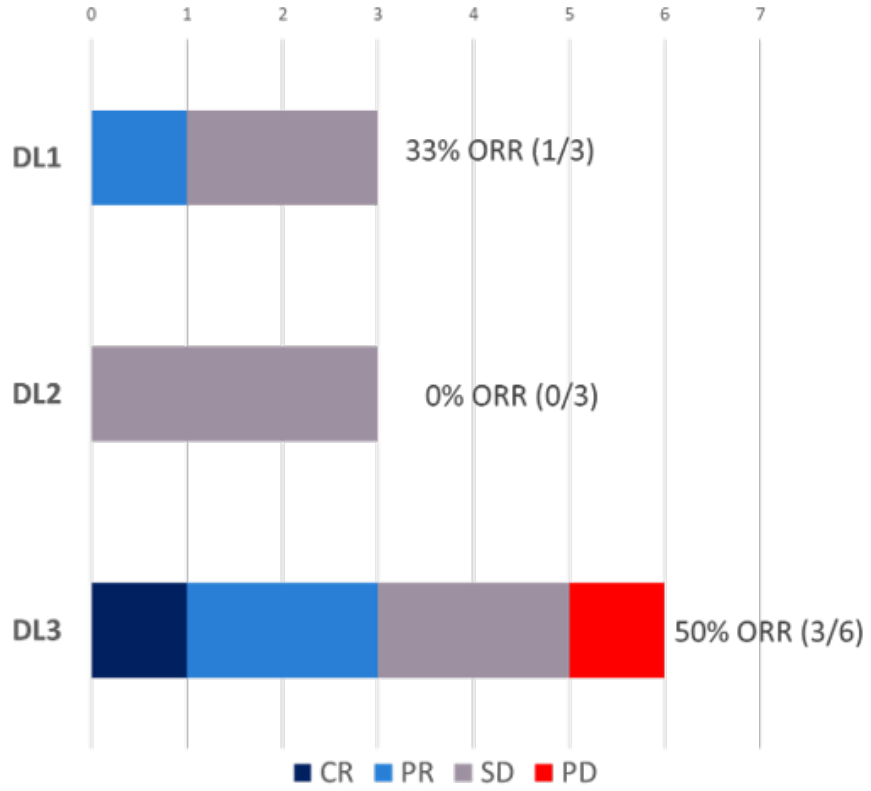
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Response Rate in Dose Escalation



Zugman *et al* ASCO GU 2026

Safety Profile

	SOC+CBM588 (N=39)		SOC (N=20)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any event	36 (92.3%)	22 (56.4%)	19 (95.0%)	10 (50.0%)
Diarrhea	20 (51.3%)	4 (10.3%)	8 (40.0%)	1 (5.0%)
Fatigue	17 (43.6%)	2 (5.1%)	10 (50.0%)	1 (5.0%)
Hyponatremia	18 (46.2%)	0 (0.0%)	9 (45.0%)	0 (0.0%)
ALT increased	15 (38.5%)	1 (2.6%)	6 (30.0%)	3 (15.0%)
AST increased	16 (41.0%)	0 (0.0%)	7 (35.0%)	2 (10.0%)
TSH increased	14 (35.9%)	0 (0.0%)	9 (45.0%)	0 (0.0%)
Hypertension	10 (25.6%)	1 (2.6%)	9 (45.0%)	1 (5.0%)
Rash maculo-papular	13 (33.3%)	1 (2.6%)	7 (35.0%)	0 (0.0%)

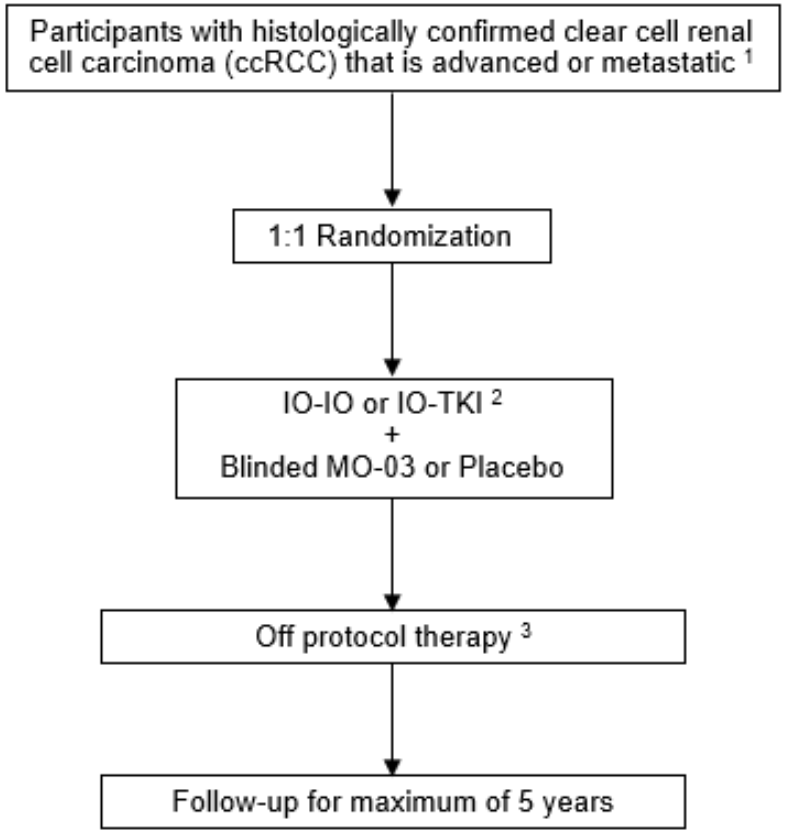
SOC, Standard of care (nivolumab/ipilimumab or nivolumab/cabozantinib); IMDC, International Metastatic renal cell carcinoma Database Consortium

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In Short

- **Unmet need in frontline ccRCC:**
  - Despite IO-IO and IO-TKI standards, primary resistance and limited durable remissions remain common.
- **Microbiome as a modifiable driver of IO response:**
  - Preclinical and clinical data (including RCC) link gut microbiome composition to immunotherapy efficacy.
- **MO-03 as a rational immune-modulating strategy**
  - MO-03 (Clostridium butyricum) is a live biotherapeutic that enhances mucosal immunity and supports favorable microbiome profiles.
- **Compelling early RCC signal with minimal toxicity**
  - Phase I studies combining MO-03 with IO-based regimens showed improved PFS and response rates without added safety risk.
- **Designed for real-world applicability**
  - Double-blind, placebo-controlled Phase III trial allowing any standard frontline IO-based regimen.
- **Safety-forward and operationally feasible**
  - Built-in safety run-in, oral administration, no systemic exposure, and low site burden.

Schema



[1] Participants with favorable risk as defined by the IMDC must plan to receive one of the tyrosine kinase inhibitor (TKI)+ immunotherapy treatment combinations as outlined in S2419 Protocol Section 7.2. They are not able to receive Regimen 1 (Ipilimumab + Nivolumab) for this study.

[2] Immunotherapy (IO) - Immunotherapy (IO) or Immunotherapy (IO) - Tyrosine Kinase Inhibitor (TKI).

[3] See S2419 Protocol Section 7.5 for criteria for removal from protocol treatment.

Study Objectives – Primary and Secondary

Primary Objective

To compare investigator assessed **progression-free survival** of participants with advanced clear cell renal cell carcinoma (ccRCC) randomized to standard of care immunotherapy (IO)-based combination regimen plus placebo versus IO-based combination regimen plus MO-03 in an intent-to-treat analysis.

Secondary Objectives

For the safety run-in: To assess the safety of MO-03 when added to each of the following standard frontline treatment regimens for advanced renal cell carcinoma: cabozantinib/nivolumab, axitinib/pembrolizumab (MK-3475) and lenvatinib/pembrolizumab (MK-3475) in the first 50 randomized patients after receiving at least two cycles of treatment.

To compare investigator assessed RECIST 1.1 response (confirmed and unconfirmed complete response and partial response) between the study arms.

To compare overall survival (OS) between the study arms.

To compare investigator assessed progression free survival (PFS) rates between the study arms at 12 months and at 24 months.

To evaluate the qualitative and quantitative toxicities between the study arms.

Stratification Factors

Participants will be randomized in a 1:1 allocation using a dynamic balancing algorithm with stratification based on:

International Metastatic RCC Database Consortium (IMDC) risk group: favorable* vs. intermediate vs. poor

Tumor with sarcomatoid / rhabdoid features: Yes vs. No

Intended SOC treatment type: IO-IO vs. IO-TKI

* Patients characterized as favorable risk may not select ipi/nivo for their SOC treatment.

Participants will be described by the following factor:

Intended SOC treatment: **(ipilimumab / nivolumab) vs. (axitinib / pembrolizumab) vs. (cabozantinib / nivolumab) vs. (lenvatinib / pembrolizumab)**

Statistical Considerations

- **Target accrual: ~718 participants** with advanced clear cell RCC randomized 1:1 (MO-03 vs placebo added to standard IO-based therapy).
- **Accrual timeline:** Expected accrual over approximately **3 years**, leveraging the full **NCTN cooperative group network** (SWOG, Alliance, ECOG-ACRIN, NRG).
- **Primary endpoint: Investigator-assessed PFS**, powered to detect a 4 month difference in median PFS with MO-03 in the intent-to-treat population.
- **Interim monitoring:**
  - **Early safety run-in** (first 50 patients on IO-TKI + MO-03) with focused AE monitoring.
  - **Formal interim efficacy/futility analyses** conducted by the SDMC at protocol-specified intervals based on number of PFS events in the pooled arms.
- **Follow-up duration:** Participants followed for **up to 5 years** for survival and long-term outcomes.

Overview of Treatments

Protocol-directed treatment components

- Systemic therapy only (no protocol-mandated surgery or radiation).
- Combination of standard-of-care (SOC) immune-based therapy plus a blinded investigational agent.

Investigational drug (MO-03)

- MO-03 (Clostridium butyricum) is a live biotherapeutic administered orally.
- Designed to modulate the gut microbiome, enhance mucosal immunity, and support immune activation relevant to checkpoint inhibitor efficacy.
- Proposed mechanism includes promotion of beneficial commensal bacteria and production of short-chain fatty acids that may augment antitumor immune responses.

Standard-of-care systemic therapy (investigator-selected)

- SOC frontline IO-based regimen, selected prior to registration:
  - IO–IO: ipilimumab + nivolumab
  - IO–TKI: axitinib + pembrolizumab; cabozantinib + nivolumab; lenvatinib + pembrolizumab
- Favorable-risk patients may not receive ipilimumab/nivolumab.
- Note: SOC regimens **cannot be switched** on study

Key Eligibility – Disease Criteria

- **Diagnosis:**
  Histologically confirmed **renal cell carcinoma (RCC) with a clear cell component** (pure or mixed histology).
- **Disease status:**
  Advanced or metastatic RCC not amenable to curative surgery or radiation.
- **SOC regimen:**
  Intended SOC treatment regimen must be decided prior to registration and may not be switched while on study.
- **Measurable disease:**
  At least **one measurable lesion per RECIST v1.1**. Participants with only bone metastases or only pleural effusions are considered evaluable disease and are eligible.
- **CNS involvement:**
  Participants with new or progressive brain metastases (active brain metastases) or leptomeningeal disease must not require immediate CNS specific treatment at the time of registration nor are anticipated to require treatment during the first cycle of therapy.

Key Eligibility – Prior/Concurrent Therapy Criteria

- **Frontline setting required:**
  - No prior systemic therapy for advanced/metastatic RCC or any treatment with immune-based combination therapy (neo/adjuvant therapy allowed if completed >12 months prior to registration).
  - Note: **Immunotherapy exposure:** No prior immune checkpoint inhibitors for metastatic disease. Prior immunotherapy (anti-PD-1, anti-PD-L1, and/or anti-CTLA-4 antibody), including neo/adjuvant IO, for any current or prior malignancy (localized disease) is allowed, if completed >12 months prior to registration.
- **OTC supplements:**
  - Participants must not plan to take any over the counter probiotic supplements at time of study registration and while on protocol treatment. Vitamin and electrolyte or mineral supplements are permitted.
- **Adrenal insufficiency:**
  - No steroid replacement therapy > 50 mg daily of hydrocortisone or prednisone equivalent dose at the time of registration.
- **Corticosteroid use:**
  - Participants must not require the use of systemic corticosteroids > 10 mg/day of prednisone or its equivalent for any reason other than replacement therapy for adrenal insufficiency.
- **Infection and Systemic antibiotics:**
  - No systemic antibiotics within 7 days prior to registration. Uncontrolled infections must be completely resolved.

Key Eligibility – Clinical Laboratory Criteria

- **Adequate organ and marrow function** within 28 days prior to registration defined as**:**
  - ✓ hemoglobin — ≥8 g/dL
  - ✓ leukocytes — ≥3 x 10^3/uL
  - ✓ absolute neutrophil count — ≥1.5 x 10^3/uL
  - ✓ platelets — ≥100 x 10^3/uL
  - ✓ total bilirubin — ≤ IULN unless history of Gilbert's disease.
    Pts. with history of Gilbert's disease must have total bilirubin ≤ 5 x IULN.
  - ✓ AST/ALT — ≤ 3 × IULN OR <5 x IULN if liver metastases are present.
  - ✓ Serum creatinine — ≤ 2 x ULN
- **Additional baseline lab tests:**
  Pts must have albumin corrected calcium and alkaline phosphatase (ALP) measured within 28 days prior to registration.
- **Cardiovascular / blood pressure:**
  No uncontrolled blood pressure or hypertension and no clinically significant, uncontrolled cardiovascular disease within 28 days prior to registration. Refer to S2419 Protocol Section 7.1g.

Treatment Administration: Allowable Concomitant Medication and Supportive Care

- **Standard supportive care permitted:**
  All institutional standard supportive measures allowed, including antiemetics, antidiarrheals, thyroid replacement, and symptom-directed care.
- **Antibiotics, PPIs, histamine-2 receptor antagonists (H2 blockers), and steroids:**
  Permitted when clinically indicated but must be recorded on the appropriate form in Rave due to potential impact on MO-03 and immunotherapy efficacy.
- **Steroid use:**
  Physiologic replacement doses allowed (e.g., adrenal insufficiency).
  Short-term steroids for immune-related adverse events permitted per standard guidelines.
- **Bone-modifying agents:**
  Denosumab or bisphosphonates allowed for patients with bone metastases per standard practice.
- **Growth factors and transfusions:**
  Allowed according to institutional guidelines.
- **Anti-hypertensive medications:**
  Participants are permitted to receive multiple anti-hypertensive medications, unless otherwise indicated in the study.

Safety Run-In – First 50 Participants Enrolled

Participating sites that enroll one of the first 50 participants to S2419 must participate in additional adverse event monitoring during the first 2 treatment cycles.

For these participants, sites will be required to assess toxicity every 3-4 weeks for the first 12 weeks.

For the First TWO (2) Treatment Cycles, sites must submit the following:

Vital Status Form

Adverse Event Form (based upon the following reporting schedule)

SOC Treatment Regimen	AE Reporting Schedule for Safety Run-in
Regimen 1: **Ipilimumab + Nivolumab (combination)** **Nivolumab alone (monotherapy)**	 Every 21 days (combo) Every 28 days (mono)
Regimen 2: Axitinib + Pembrolizumab (MK-3475)	Every 21 days
Regimen 3: Cabozantinib + Nivolumab	Every 28 days
Regimen 4: Lenvatinib + Pembrolizumab (MK-3475)	Every 21 days

Adverse Events meeting the definition of a Serious Adverse Event, as defined in S2419 Protocol Section 8.6, must follow the expedited reporting requirements outlined in Section 8.6.

After Cycle 2, Adverse Event Reporting will be done once per Cycle.

Disease Assessment Timing, Frequency & Modality

Timing: Disease assessment timing is based on calendar timing counted as weeks after registration (not based on cycles or drug administration).

Frequency

- Prior to randomization (baseline).
- Prior to Progression (both during treatment and after off all components of protocol treatment):
  - Disease assessments must be done every 12 weeks (± 2-week window).
- After progression:
  - For participants off all components of protocol treatment:
    Disease assessment is at the discretion of the treating investigator. Follow-up will occur every 6 months for the first 2 years after randomization, then annually for Years 3-5.

Modality: Disease should be assessed in the same manner as done at baseline.

Disease Assessment - Required Assessments

Baseline assessments

- Radiographic disease assessment prior to treatment initiation using CT/MRI per RECIST v1.1, including:
  - CT of chest/abdomen/pelvis or MRI for tumor assessment within 28 days prior to registration.
  - If suspected brain metastases: Brain MRI within 28 days prior to registration.
  - If suspected bone metastases: Bone scan within 42 days prior to registration.

Required Imaging at Each Subsequent Disease Assessment Timepoint

- CT of chest with contrast (without contrast if CT contrast is not tolerated by the participant)
- CT or MRI of abdomen and pelvis with contrast
- If participant has bone metastases: Bone scan

Central Radiology Review

- Local investigator/site radiology review used for treatment decisions and primary endpoint determination.
- Blinded Independent Central Review (BICR) performed retrospectively for selected analyses. Not required for real-time treatment management.

Clinical Assessments

- Disease status, performance status, and toxicity assessed at each protocol-defined clinic visit.

Progression Confirmation

- Disease progression determined per RECIST v1.1; confirmatory scans obtained when clinically appropriate.

Post-treatment Follow-up

- After treatment discontinuation, participants followed for subsequent therapy and survival for up to 5 years.

Anticipated Adverse Events – Experimental Therapy (MO-03)

Category	Anticipated Events (MO-03–Specific)	Notes / Mitigation
Gastrointestinal	Nausea, abdominal bloating, flatulence, constipation, upper abdominal pain, diarrhea	Generally low grade; distinguish from IO-related colitis
Infectious (rare)	Bacteremia, sepsis (very rare; post-marketing reports)	Primarily in patients with comorbidities or concomitant meds
Musculoskeletal	Joint and muscle pain	Most events are low grade and manageable; evaluate for IO-related etiology
Vascular	Hypertension	Primarily VEGF-TKI–related; manage per standard antihypertensive guidelines.
Hypersensitivity	Rash, urticaria, allergic reaction (rare)	Discontinue MO-03 if suspected
Metabolic / Microbiome-related	Anorexia, Potential interaction with antibiotics, PPIs, steroids	Concomitant meds prospectively captured
Drug interaction (theoretical)	Altered vitamin K production (e.g., warfarin interaction)	No routine anticoagulation restrictions; clinical monitoring

Additional Monitoring

- No additional laboratory or imaging monitoring required beyond standard IO-based therapy.
- Enhanced **safety surveillance during initial safety run-in** period.
- **Concomitant antibiotics, PPIs, and steroids documented** due to microbiome relevance.

Possible Serious Adverse Events – Experimental Therapy (MO-03)

SAEs to Watch For	Rationale / Context	Monitoring / Action
Bacteremia / Sepsis (very rare)	Reported in post-marketing experience with live biotherapeutics; primarily in patients with comorbidities or concomitant medications	Immediate SAE reporting; discontinue MO-03; manage per institutional standards
Anaphylaxis / Severe hypersensitivity	Rare post-marketing reports	Permanent discontinuation of MO-03; standard emergency management
Severe gastrointestinal intolerance	Distinct from IO-mediated colitis; may present as severe diarrhea or abdominal symptoms	Hold MO-03; evaluate to exclude immune-mediated toxicity
Unexpected infection signal	Theoretical risk related to live bacterial product	Enhanced vigilance during early treatment; DSMC oversight

Additional Safety Oversight

- **Early safety run-in** with focused SAE surveillance during initial treatment phase.
- Independent **DSMC review**.
- No additional routine labs or imaging required beyond standard IO-based therapy.

Criteria for Removal from Protocol Treatment

Removal from blinded study agent (MO-03 / placebo)

- Progression
- Completion of **3 years post-registration**
- Initiation of **non-protocol systemic anti-cancer therapy**
- **Unacceptable toxicity**
- **Treatment delay > 84 calendar days** for blinded study agent
- **Participant withdrawal**

Removal from SOC treatment regimen

- Progression
- Completion of assigned **SOC regimen** (see S2419 Protocol Section 7.2)
- Initiation of **non-protocol systemic anti-cancer therapy**
- **Unacceptable toxicity**
- **Treatment delay > 90 calendar days** for both SOC agents
  (If one SOC agent continues, participant may remain on treatment)
- **Participant withdrawal**

Operational note

- SOC regimens **cannot be switched** on study
- Blinded study agent may continue alone (up to 3 years) if SOC regimen is stopped, no new systemic therapy is initiated, and none of the other criteria above are met.

Discontinuation of Treatment

- All reasons for discontinuation of treatment must be documented in the Off Treatment Notices.

Participant Registration

Registration platform
- Participants registered via OPEN using protocol-specific eligibility confirmation.
- No exceptions to SWOG registration policies are permitted.

Timing of treatment start
- Initiation of treatment with the blinded study drug must be planned to start no more than 14 calendar days after randomization and may occur on the same day as the initiation of SOC therapy, but this is not required.
- Initiation of treatment with the SOC immune-based combination therapy must be planned to start within +/- 14 calendar days of start of blinded study drug.
- Sites should ensure study drug availability prior to registration to avoid delays.

Drug ordering considerations
- MO-03/placebo must be ordered after registration; no starter supplies are available.
- Allow up to 5 business days (after submission of the drug order request form to McKesson) for study drug to arrive.

Washout considerations
- All prior therapies must meet protocol-defined washout periods before registration and treatment initiation.
- Specimen / kit readiness
- Baseline biospecimen collection required; sites must confirm availability of protocol-specific collection kits prior to treatment start.

Central review
- No central pathology or radiology review required for eligibility or registration.
- Central imaging review conducted post-enrollment for selected analyses only.

Multiple registration steps
- Single registration step; no secondary randomization or re-registration required.

S2419 Unique Data Submission Forms & Timepoints

<table>
<tr><th>Atypical Data Submission Forms/Frequency:</th><th>Submission Timepoint(s)</th></tr>
<tr><td>Safety Run-In (first 50 randomized participants):
Additional adverse event monitoring and submission of Vital Status and Adverse Event Forms during the first 2 cycles (12 weeks) of treatment.</td><td>For the first 50 randomized participants during the first 2 treatment cycles (12 weeks), safety run-in data submission to be based on the following schedule:
<table>
<tr><th>SOC Treatment Regimen</th><th>AE Reporting Schedule for Safety Run-in</th></tr>
<tr><td>Regimen 1:
Ipilimumab + Nivolumab (combination)
Nivolumab alone (monotherapy)</td><td>
Every 21 days (combo)
Every 28 days (mono)</td></tr>
<tr><td>Regimen 2:
Axitinib + Pembrolizumab (MK-3475)</td><td>
Every 21 days</td></tr>
<tr><td>Regimen 3:
Cabozantinib + Nivolumab</td><td>
Every 28 days</td></tr>
<tr><td>Regimen 4:
Lenvatinib + Pembrolizumab (MK-3475)</td><td>
Every 21 days</td></tr>
</table></td></tr>
<tr><td>S2419 Antibiotic PPI Steroid Form
Concomitant Medications Form</td><td>Within 30 days after each cycle of treatment
Within 30 days after discontinuation of all components of protocol treatment</td></tr>
</table>

Specimen Submission

With participant consent, specimens must be submitted to the SWOG Biospecimen Bank– Solid Tissue, Myeloma and Lymphoma Division, Lab #201 (Email: bpcbank@nationwidechildrens.org) at the following timepoints. Specimens must be labeled in accordance with the Specimen Labeling Requirements. Standard label templates are accessible from the SWOG Specimen Labeling webpage.

Specimen Type	Amount / Description	Collection Timepoints	Kit Provided?	Additional Instructions
Peripheral whole blood	• 20 mL peripheral blood collected in two 10 ml EDTA tubes	• Baseline (after S2419 registration and prior to initiation of treatment) • 12 weeks (+/- 7 days) • Progression (+ 7 days) IMPORTANT: After collection: • **Do not freeze.**	No; Sites will use institutional supplies.	• Follow the Specimen Collection and Handling Guidelines for Whole Blood. • Ship ambient the same day as collected (M-F) if possible, or the next working day. • Do not ship on a Saturday or the day prior to a holiday. • If blood is stored >24 hrs., note the storage time in the Specimen Tracking System.
Peripheral whole blood	• At least 8.5 mL peripheral whole blood collected in each of two 10 ml Streck cfDNA tubes	• Baseline (after S2419 registration and prior to initiation of treatment) • 12 weeks (+/- 7 days) • Progression (+ 7 days) IMPORTANT: After collection: • **Do not refrigerate.** Do not process.	Yes; Order kits online. Allow 7 days after order for receipt of shipment.	
Stool	• 0.5-1 gm per kit Participants may collect sample at home and deliver at their next appointment. **IMPORTANT**: Instruct participants to store the sample at room temperature and record date of sample collection. (See next slide)	• Baseline (after S2419 registration and prior to initiation of treatment) • 12 weeks (+/- 7 days) • Progression (+ 7 days) IMPORTANT: After collection: • **Do not refrigerate.**	Yes; Order kits online. Allow 7 days after order for receipt of shipment.	• **Follow the instructions included in the Omnigene-Gut kit** (that will be included with the specimen collection kit). • For each timepoint, samples must be returned to the clinic and shipped to the SWOG Biospecimen Bank **within 45 days after collection.**
FFPE archival tissue	• 1 FFPE Tissue block OR • Minimum of 20 positively charged, unstained, air-dried (5 micron) FFPE slides from 1 FFPE tissue block • 1 H&E section (4-7 microns), if available from the submitted FFPE tissue block.	Baseline sample (archival tissue from the most recent diagnostic sample) • Submit within 30 days after registration.	No; Sites will use institutional supplies.	Follow the Specimen Collection and Handling Guidelines for FFPE Tissue. The partially redacted pathology report corresponding to the archival tissue must be submitted with the tissue. Follow the pathology report requirement guidelines.

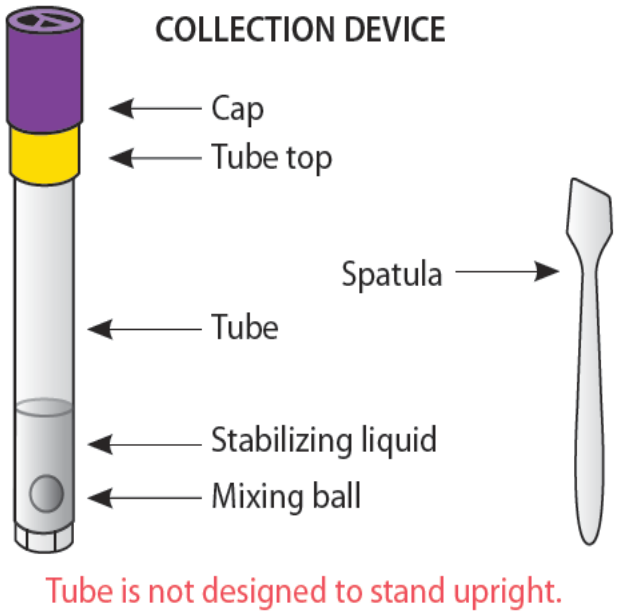
Stool Sample Collection (1)



Participants may collect samples at home (within 7 days prior to the next timepoint) and return the sample to the clinic with their next visit.

OMNIgene GUT OMR-200 collection kits will be provided and will include:

- OMNIgene GUT (OMR-200) collection kit, specimen bag, and return shipping box
- OMNIgene GUT collection instructions
- Site-facing instructions: S2419 Stool Shipping Instructions (accessible via S2419 Protocol abstract page on the CTSU website under Documents >> Protocol Related Documents >> Supplemental)
- Participant-facing (CIRB-approved): S2419 Supplemental Collection Instructions for Participant (accessible via S2419 Protocol abstract page on the CTSU website under Documents >> CIRB Approved Documents >> Support Documents



Please provide the participant with the S2419 Supplemental Collection Instructions for Participant and verbally inform participants of the allowable collection window and review the instructions on the form with the participant.

Stool Sample Collection (2)
Site Receipt and Shipping

When the participant provides the stool sample to site staff:

- Verify that specimen is properly labeled and includes the collection date.
  - If the collection date is missing or illegible, please ask the participant for the date and clearly rewrite it on the tube.
- Keep the sample at room temperature until shipment.
- Enter the specimen into the SWOG Specimen Tracking System.
- Package and ship the stool sample to the SWOG Biospecimen Bank at ambient temperature following directions below.
- Ship samples within 1-2 business days of receiving them from the participant.

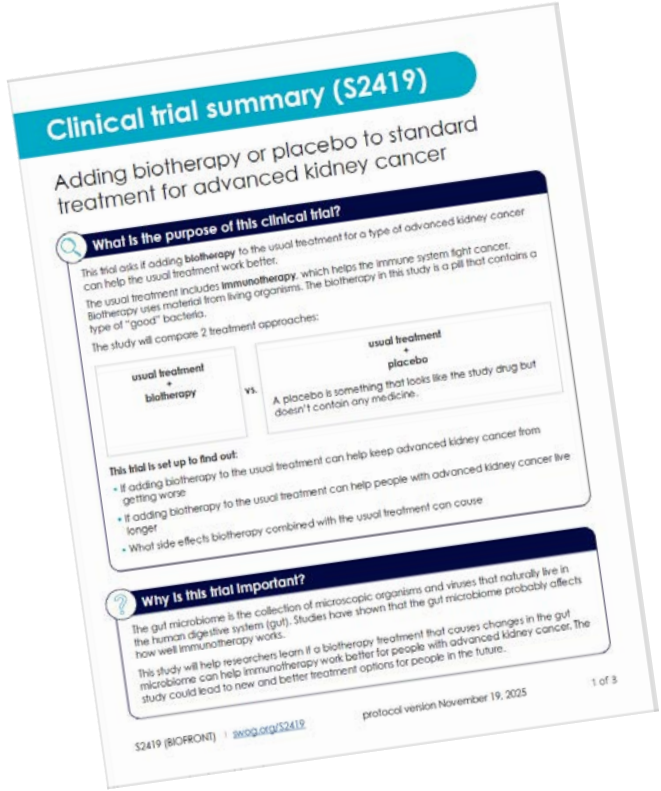
The sample should be shipped to the SWOG Biospecimen Bank within 45 days of collection.

Stool samples from more than one participant may be included in the same shipment if all samples are appropriately labeled, a packing list is included for each sample, and samples for each participant are separated within the shipper.

Resources and Materials — Patient-Friendly Clinical Trial Summary

The Patient-Friendly Summary is an educational tool to share key information about the trial

- Easy to understand, written in plain language
- Explains why the study is important, study treatments, who is eligible, length of trial involvement, costs, and how to learn more
- May include graphics to illustrate study design or treatments
- Translated into Spanish


Clinical trial summary (S2419)

Adding biotherapy or placebo to standard treatment for advanced kidney cancer

What is the purpose of this clinical trial?

This trial asks if adding **biotherapy** to the usual treatment for a type of advanced kidney cancer can help the usual treatment work better.

The usual treatment includes **immunotherapy**, which helps the immune system fight cancer. Biotherapy uses material from living organisms. The biotherapy in this study is a pill that contains a type of "good" bacteria.

The study will compare 2 treatment approaches:

usual treatment + biotherapy vs. usual treatment + placebo

A placebo is something that looks like the study drug but doesn't contain any medicine.

This trial is set up to find out:

- If adding biotherapy to the usual treatment can help keep advanced kidney cancer from getting worse
- If adding biotherapy to the usual treatment can help people with advanced kidney cancer live longer
- What side effects biotherapy combined with the usual treatment can cause

Why is this trial important?

The gut microbiome is the collection of microscopic organisms and viruses that naturally live in the human digestive system (gut). Studies have shown that the gut microbiome probably affects how well immunotherapy works.

This study will help researchers learn if a biotherapy treatment that causes changes in the gut microbiome can help immunotherapy work better for people with advanced kidney cancer. The study could lead to new and better treatment options for people in the future.

S2419 (BIOFRONT) | swog.org/S2419 protocol version November 19, 2025 1 of 3

We recommend a study team member review the summary with the patient as an introduction to the trial, or alongside the consent

- Also available as a PDF to be printed or shared electronically

The summary is accessible from:

- **swog.org/S2419** (publicly accessible link, with printable PDF)
- Also via the S2419 protocol abstract page on the CTSU website under Documents >> CIRB Approved Documents >> Support Documents, listed as “Clinical Trial Summary” (login required)

FAQs - Eligibility

Can participants who screen fail be re-screened?

If a participant is registered to the study (in OPEN) and then it is discovered that they are ineligible, no. They may not be taken off study and registered to the study again at a later date.

What is the rationale for the eligibility criterion that participants cannot have a blood pressure of SBP over 140 or a DBP over 90 within 28 days of registration?

The BP requirement was incorporated because patients may receive anti-VEGF-directed therapy, which causes or increases risk of hypertension. Ensuring that BP is adequately controlled before study entry helps minimize the risk of treatment-related cardiovascular complications.

FAQs - Treatment

May we use subcutaneous pembrolizumab as an alternative to IV pembrolizumab for patients receiving Regimens 2 or 4?

No, not at this time. Route of administration for all protocol treatment must match what is specified in section 7 of the protocol.

For patients on q 4-week Nivolumab therapy, the q 6-week toxicity notation and dispensation of MO-03/placebo will not align with SOC Nivolumab appts. Concerns of fees associated with more frequent visits than SOC requirement. Ok for toxicity notation and drug dispensation q 4-weeks?

Acceptable to dispense an extra bottle at their current visit if needed to get the patient through to the next visit. For toxicity review, acceptable to do visits q 4 weeks as long as SOC safety labs are performed at least once in the 42-day protocol-defined cycle length.

Where can we find the Investigators Brochure for SWOG-Held IND Agent: Blinded Drug MO-03 or placebo (NSC-854485)?

Since SWOG holds the IND for this study, section 3 of the protocol serves as the IB for the blinded agent.

FAQs – Drug Accountability

The participant intake calendars in S2419 Protocol Section 18 only include Days 1-11. What should participants use to document drug intake for Days 12-42?

Additional Participant Intake Calendar pages (Days 12-42) are accessible via the S2419 protocol abstract page CTSU website under Documents >> Protocol-Related Documents>>Supplemental Documents, listed as "S2419 Intake Calendar Additional Pages" (login required).

Where can we find the Drug Accountability Record Form (DARF)?

The Oral Drug Accountability Record Form (DARF) can be found here: https://dctd.cancer.gov/research/ctep-trials/for-sites/agent-management/accountability-record-oral.pdf.

For more information refer to: DARF FAQs and DARF training, accessible from the NCI Agent Management webpage (https://dctd.cancer.gov/research/ctep-trials/for-sites/agent-management).

Where can we find the MO-03 Investigator's Brochure?

MO-03 is provided under a SWOG-held IND, wherein the SWOG protocol serves as the Investigator Brochure per SWOG Policy 15. In cases where the Investigator Brochure for MO-03 is required by the site's IRB of record, requests may be submitted to the CTSU website by completing the **CTSU Request for Clinical Brochure Form**, accessible via the **S2419** protocol abstract page on the CTSU website under Documents >> Protocol Related Documents >> Pharmacy

Actual Accrual N=30 (as of Sep 29, 2026)







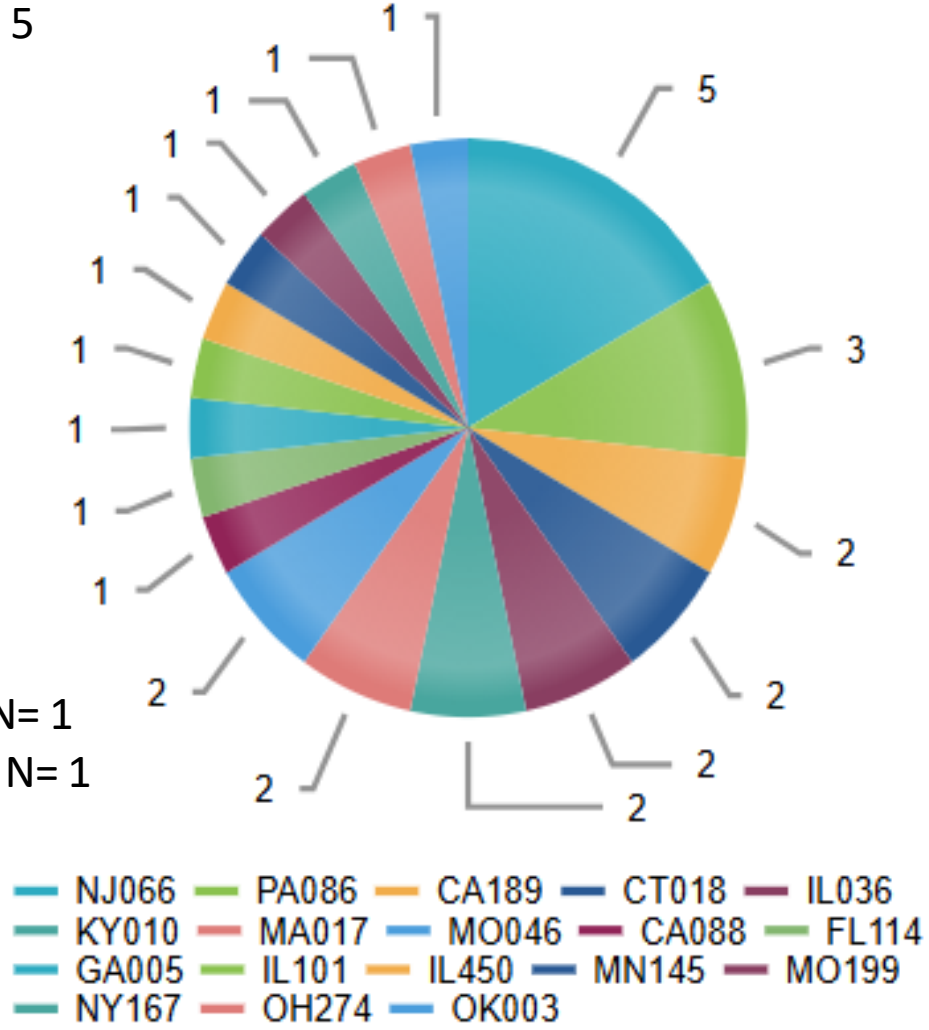
Biren Saraya

Andre Kidd

David Braun

Patient Intervention Accrual by site

1. Rutgers Cancer Institute of New Jersey, N= 5
2. Fox Chase Cancer Center, N= 3
3. UC Davis, N= 2
4. Lahey Clinic, N= 2
5. Yale University, N= 2
6. University of Kentucky, N= 2
7. Northwestern University, N= 2
8. Missouri Baptist Medical Center, N= 2
9. UC Irvine Health, N= 1
10. Minnesota Oncology, N= 1
11. Parkland Health Center, N= 1
12. Northwestern Medicine Orland Park, N=1
13. UHHS-Chagrin Highlands Medical Center, N= 1
14. Univ of Oklahoma Health Sciences Center, N= 1
15. Emory University Hospital, N= 1
16. Illinois Cancer Care-Peoria, N= 1
17. The Watson Clinic, N= 1
18. University of Rochester, N= 1



Advantages of This Study in RCC

- An easy, less toxic way of improving clinical outcomes
- Very easy to accrue
- Appealing trial to patients and providers and patient advocacy groups
- First study in NCTN to evaluate microbiome intervention
- Far reaching application in future across multiple tumor types where immune checkpoint inhibitor is used

Patient Advocacy Perspective

BIOFRONT represents the kind of innovative research patients need: exploring whether we can use biotherapy to modify the gut microbiome and potentially enhance a patient's response to cancer treatment. As a former clinical trial participant and metastatic kidney cancer survivor, I know the power of research to change lives, and patients deserve every opportunity to make tomorrow better than today.

Laura Esfeller, Patient Advocate SWOG

Contact Information

Eligibility, RAVE, Data or Specimen Submission:	SWOG Statistics and Data Management Center E-mail: guquestion@crab.org or Phone: 206/652-2267
Regulatory, Protocol, Informed Consent:	SWOG Network Operations Center E-mail: protocols@swog.org or Phone: 210/614-8808
Medical Queries (treatment or toxicity related questions):	E-mail: S2419medicalqueries@swog.org
Specimen Collection Kit Questions:	E-mail: bpcbank@nationwidechildrens.org
Specimen Tracking System (STS) Amendments, Errors, Connectivity Issues and Technical issues with the SWOG CRA Workbench:	E-mail: technicalquestion@crab.org
Source Documentation Portal – Central Monitoring	E-mail: centralmonitorquestion@crab.org
Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) (new account requests, reset password)	Refer to: CTEP Registration and Access Management
Access to iMedidata Rave or Delegation of Task Log (DTL), Oncology Patient Enrollment Network (OPEN) questions	See Protocol Sections 14.3 or 13.5 or contact the CTSU Help Desk at: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
TRIAD image submission questions:	E-mail: swog2419@irocohio.org
Serious Adverse Event Reporting questions:	See Protocol Section 8.6 or Email: adr@swog.org
Emergency Unblinding:	See Protocol Section 18.10 for Emergency Unblinding Contact Information and Procedures. Direct informational questions to: guquestion@crab.org. Direct medical questions pertaining to emergency unblinding to one of the Study Chairs at contact information indicated in Protocol Section 18.10.

Open Forum Discussion – Questions and Answers

Thank you

- Scan the QR code

  or follow the link below

  to download the

  S2419 Kick Off Meeting Handout and Slide Set



https://www.swog.org/S2419-F26handouts

The meeting recording will be posted in ~3-4 weeks via the SWOG Members' website and via the CTSU CLASS learning management system, as a resource link under the current S2419 Required Site Initiation Training course (login required).