

Cancer and Complementology

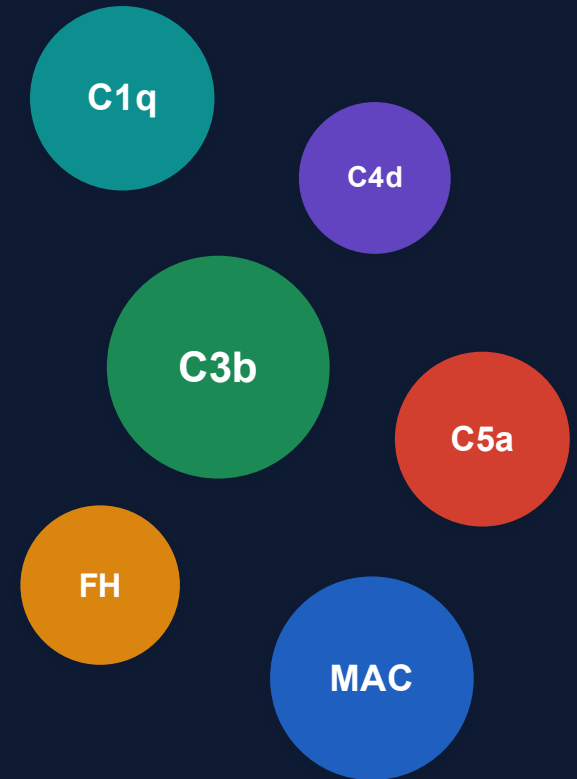
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Disclosures

- Scientific Advisory Board, Alexion Astra Zeneca Rare Disease
- Scientific Advisory Board, Novartis Pharmaceuticals
- Consultant, Apellis Pharmaceuticals
- Consultant, Amgen Pharmaceuticals
- Royalty, UptoDate

Several agents discussed are used off-label in cancer-associated TMA. I will flag where evidence is observational.

Objectives

- 1 Explain why complement is antitumor in one cancer and protumor in another and what decides it.
- 2 Show what changed: local, tumor-cell and intracellular complement, using kidney cancer as the worked example.
- 3 Classify complement in a cancer patient with kidney injury as driver, amplifier, biomarker, or bystander.
- 4 Apply that classification to TMA, TA-TMA, and monoclonal gammopathy

The same molecule can kill a tumor cell or destroy a glomerulus

Complement is activated in almost every sick cancer patient. That doesn't make it the diagnosis.

01 The system changed

Complement is no longer a liver-made serum cascade. It is made locally in tumors, acts on membranes, and operates inside cells - where the cascade may not be involved at all.

02 The tumor

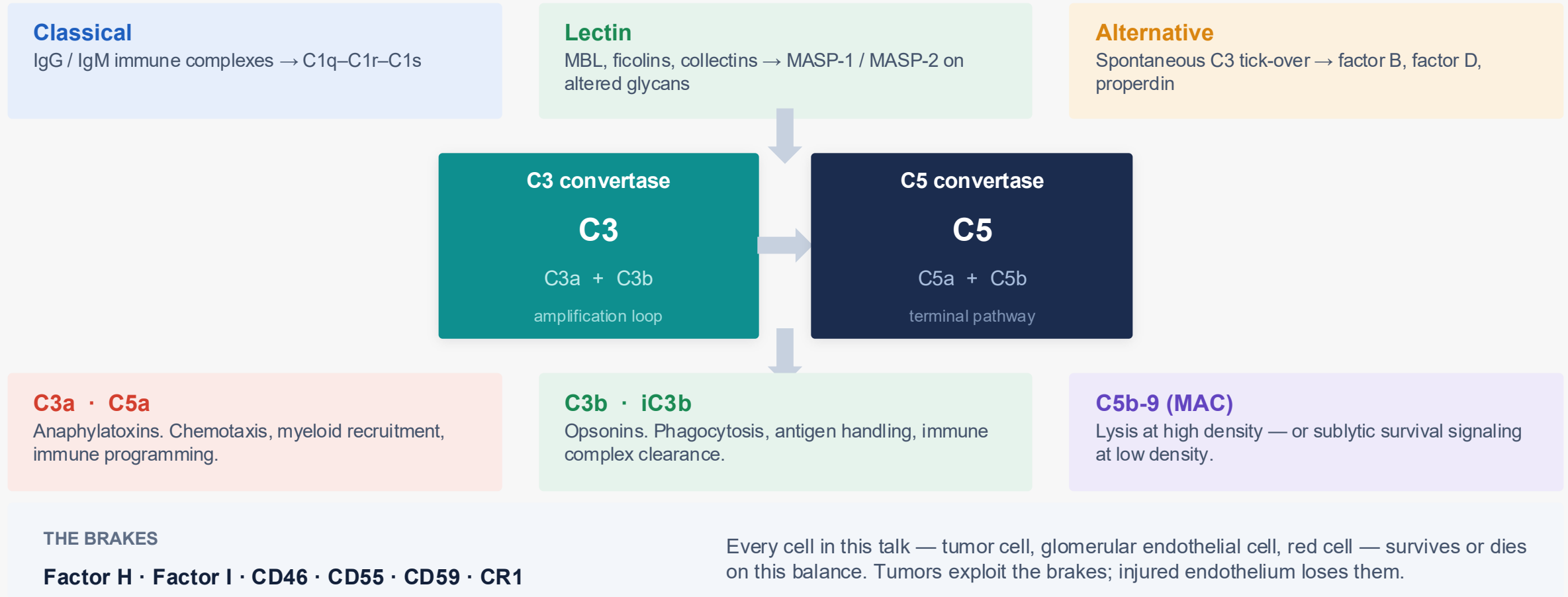
Antitumor in some cancers, protumor in others - with hazard ratios pointing in opposite directions across tumor types. Kidney cancer is the clearest worked example.

03 The patient

In a cancer patient with AKI, hemolysis, or biopsy TMA, complement may be the driver, an amplifier, a biomarker of injury, or an innocent bystander. Only one of those is a drug target.

Three doors, one amplification loop, and a set of brakes

The only structure you need for the next twenty minutes.



One goal: deposit clusters of C3b on a surface. Everything else follows from where that happens, who made the C3, and which brake is missing.

Outside the cell, on the membrane, and inside the cell

The serum-cascade model is necessary but no longer sufficient — least of all in cancer.

1905

The cascade

Extracellular, liver-derived, activation-and-lysis.

2013

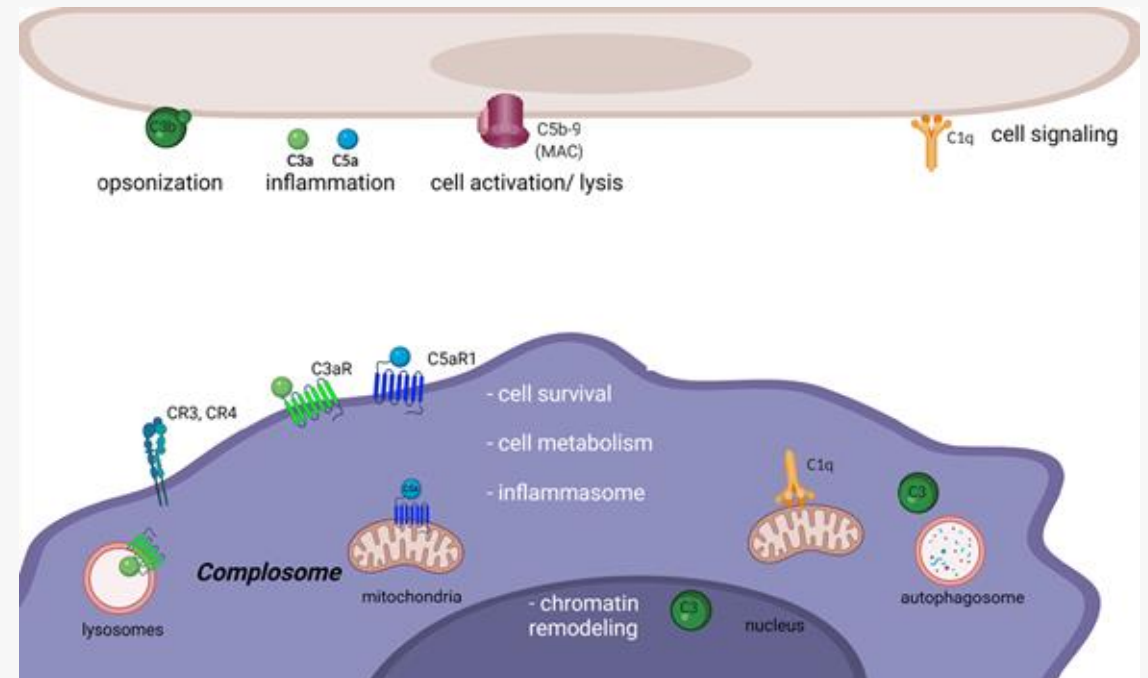
The complosome

C3 and C5 fragments signaling inside the cell — metabolism, survival, autophagy, T-cell function.

2020s

Tumor-cell complementology

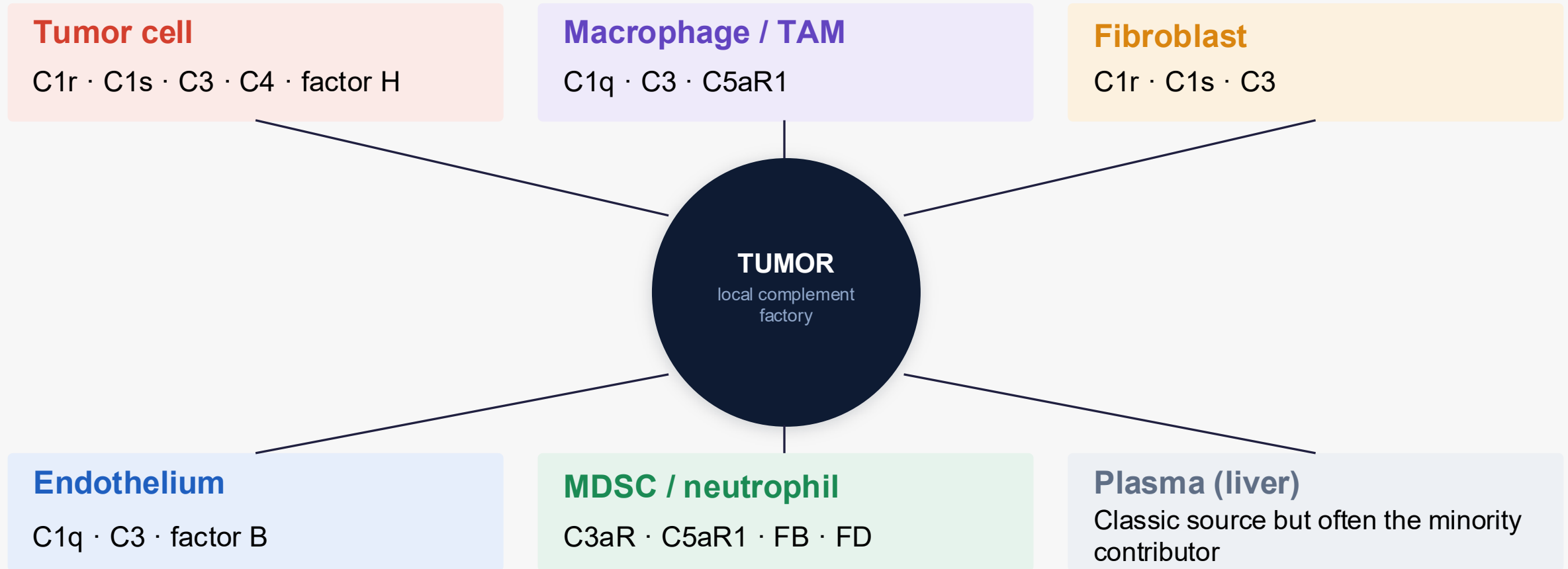
Tumor and stromal cells make, retain, and use complement proteins with no cascade involved.



Three coordinates now define any complement statement in cancer — WHERE is it acting (plasma, membrane, cytosol), WHO made it (liver, or the tumor next to it), and IS THE CASCADE INVOLVED AT ALL?
A routine complement panel answers only the first half of the first question.

Tumors are complement-rich ecosystems

They do not wait for the liver. Complement here is made locally, by several cell types at once, and consumed locally.



Serum complement can look unremarkable while the tumor is a furnace. That is one reason plasma assays underperform as tumor biomarkers.

The same system restrains cancer and promotes it

These are not contradictory findings in the literature. They are different microenvironments.

+ Complement restrains the tumor

- Complement-dependent cytotoxicity after therapeutic mAbs (anti-CD20, anti-CD38, anti-GD2)
- Opsonophagocytosis and clearance of dying tumor cells
- Antigen handling and presentation
- Tumor-intrinsic C1r/C1s driving chemokine secretion and cytotoxic T-cell infiltration in TNBC — higher expression, better survival

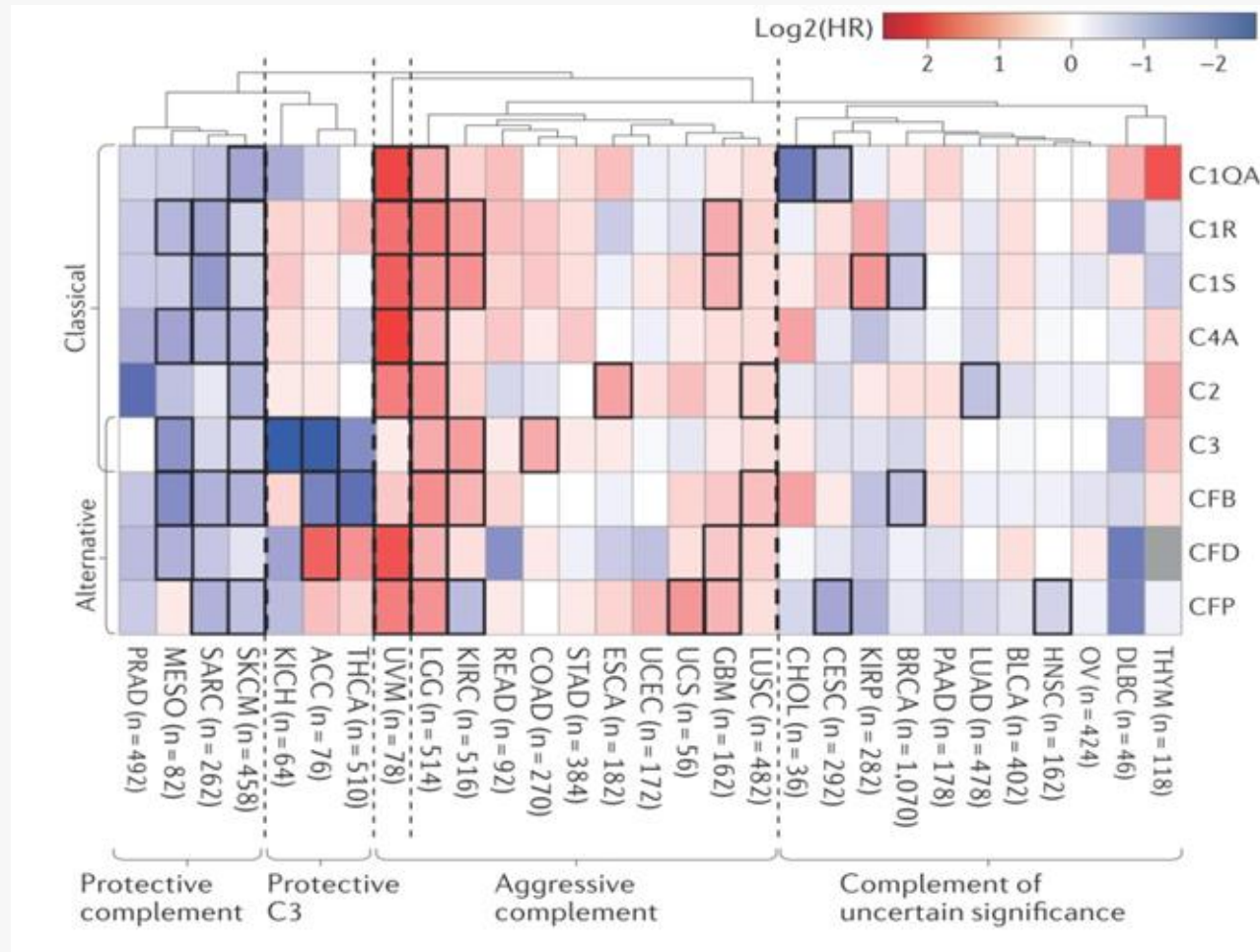
– Complement promotes the tumor

- Chronic C3a/C5a signaling recruits MDSCs and tumor-associated macrophages
- CD8 T-cell exclusion and exhaustion
- Angiogenesis, EMT, invasion, and pre-metastatic niche formation
- Sublytic C5b-9 delivering PI3K/AKT survival signals instead of lysis
- CD46/CD55/CD59 and recruited factor H shielding the tumor from antibody therapy

The pattern that predicts which side wins: acute, antibody-driven, opsonin-and-MAC complement tends to be antitumor. Chronic, myeloid-driven, anaphylatoxin-dominated complement tends to be protumor.

“Context-dependent” is a data statement, not a hedge

Nine complement genes, thirty tumor types, hazard ratios pointing in opposite directions.



Red = higher risk

High expression of that complement gene predicts worse survival in that cancer.

Blue = protective

The identical gene predicts better survival elsewhere - melanoma, sarcoma, mesothelioma, prostate.

KIRC sits in “aggressive complement”

Clear-cell RCC (n = 516) clusters with the tumors where complement expression tracks worse outcomes. That is why the next four slides are about kidney cancer.

There is no such thing as “the role of complement in cancer.” The answerable question is - which gene, which tumor, which compartment.

How C5a turns inflammation into immune silence

The best-established protumor circuit and the reason complement blockade was ever proposed in oncology.



WHY IT MATTERS

C5a is not an inflammatory by-product in a tumor. It behaves like an immunologic brake recruiting and programming the suppressive myeloid compartment that keeps cytotoxic T cells out.

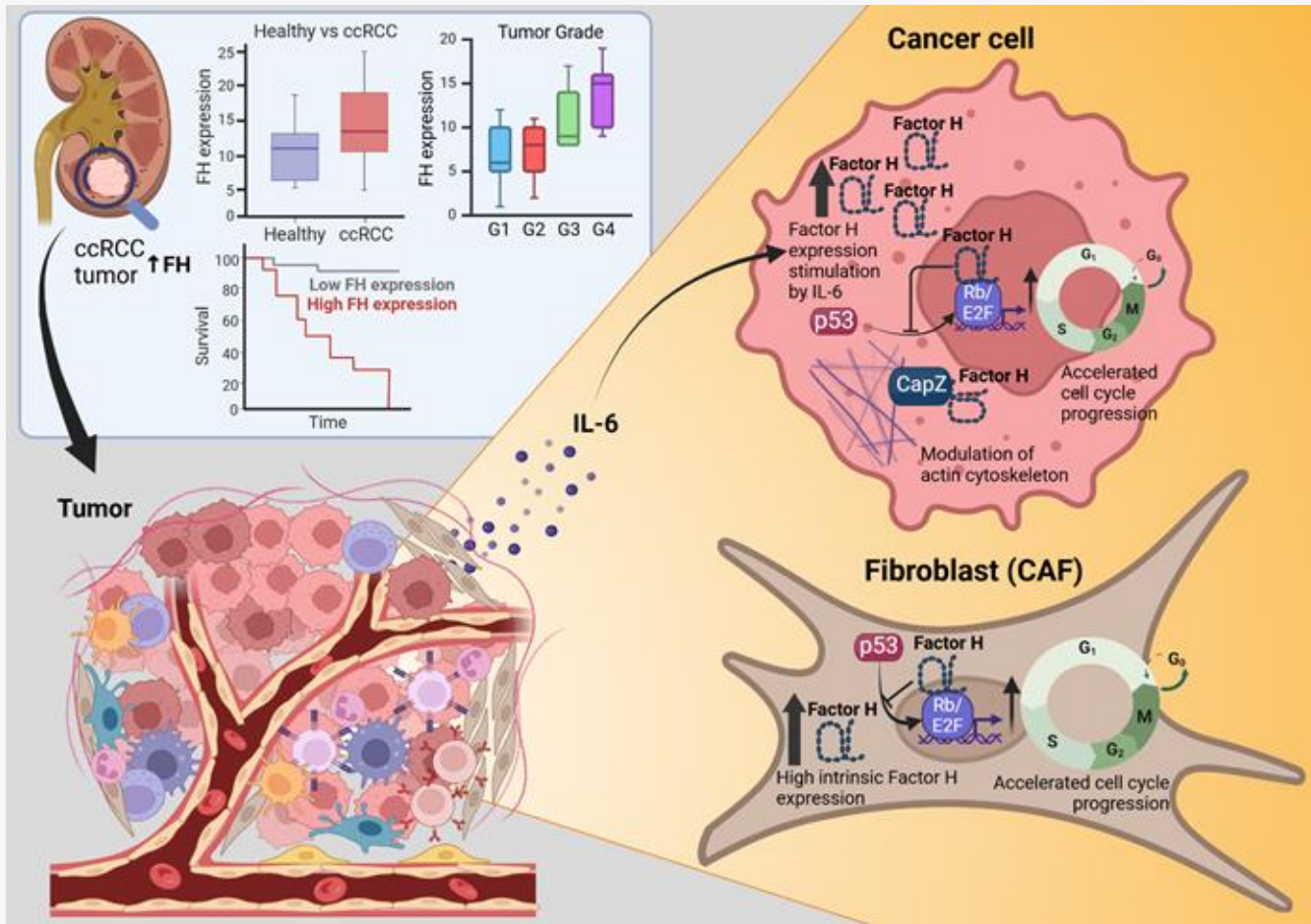
THERAPEUTIC LOGIC

Block C5a/C5aR1 to release the brake — most plausibly combined with PD-1/PD-L1 blockade or radiotherapy, and most plausibly in myeloid-rich tumors. Preclinically this works. Clinically, see slide 12.

Note what this predicts: inhibiting complement here would help the tumor-bearing patient - the opposite of everything the second half of this talk will argue about the kidney.

Factor H inside a tumor cell is not regulating complement

The textbook brake on C3 convertase, acting as a nuclear cell-cycle protein in clear-cell RCC.



Expression tracks aggressiveness

Factor H is higher in ccRCC than healthy kidney and rises stepwise from grade 1 to grade 4. High tumor CFH expression predicts shorter survival — also in lung adenocarcinoma.

The mechanism is intranuclear

Factor H interacts with Rb/E2F and restrains p53, accelerating cell-cycle progression. IL-6 from the microenvironment drives its expression in both tumor cells and cancer-associated fibroblasts.

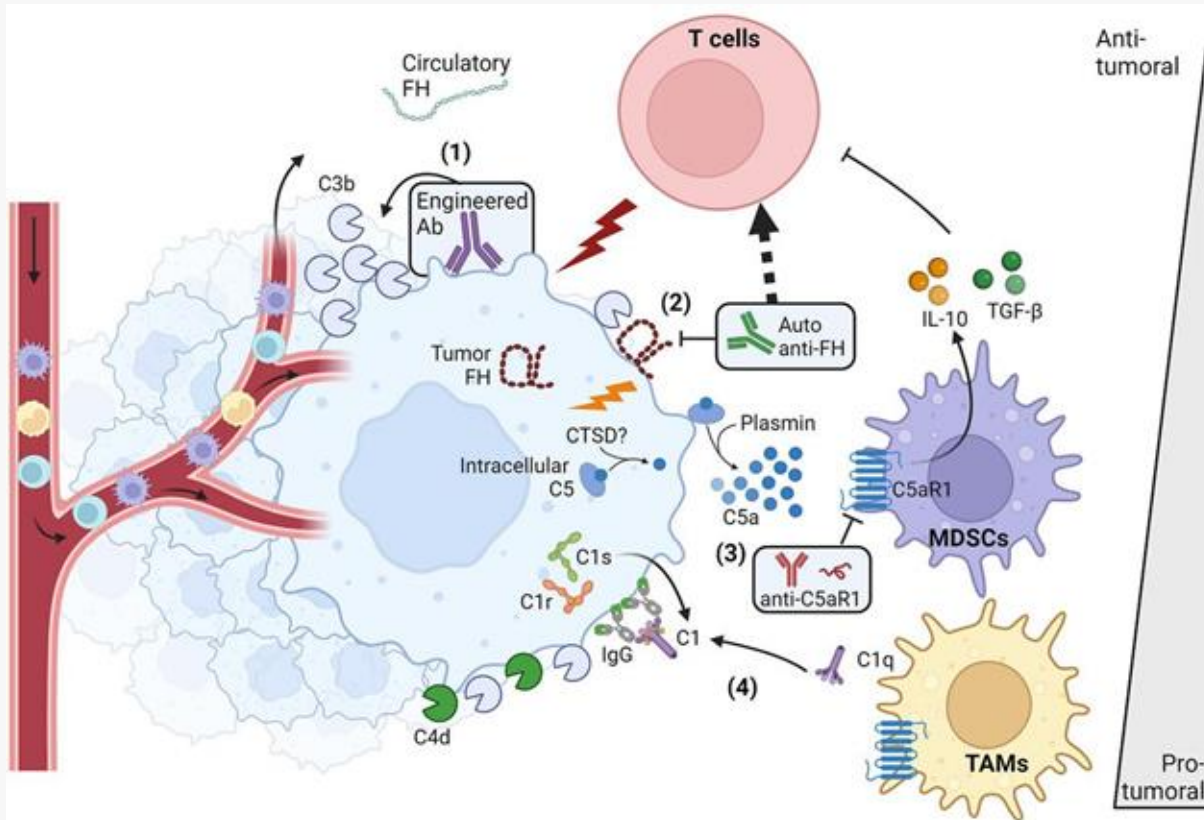
Silencing CFH changes the phenotype

Knockdown reduced proliferation, viability and migration — with no extracellular cascade involved.

A complement regulator can be a tumor-cell oncoprotein. You cannot infer its biology from its textbook extracellular job.

Do we block complement in cancer? Only if you can name which one

Three coherent strategies, pointing in opposite directions and one sobering trial.



Antitumor at the top, protumor at the bottom: engineered antibodies and anti-factor-H enhance killing, while anti-C5aR1 removes the myeloid brake.

A Boost complement
Fc engineering, blocking CD55/CD59, targeting tumor-recruited factor H make antibody therapy kill better.

B Inhibit selectively
C5a/C5aR1 or C3aR blockade with checkpoint inhibition, in myeloid-rich tumors.

C Target tumor-intrinsic complement
C1s, intracellular factor H - cell-permeable or tumor-delivered agents. Earliest stage.

STELLAR-001: Avdoralimab (anti-C5aR1) with durvalumab in advanced solid tumors was stopped for insufficient clinical benefit. The lesson is patient selection, not that the biology was wrong.

Four roles. Only one of them is a drug target.

In a cancer patient with kidney injury, name the role before you name the drug.

DRIVER

Complement dysregulation is necessary for the phenotype.

Complement-mediated TMA in a susceptible host · C3G / MPGN driven by a clone

→ **Block complement**

AMPLIFIER

Something else injures endothelium; complement escalates the injury.

TA-TMA after HSCT · a subset of gemcitabine and carfilzomib TMA

→ **Remove the trigger first, then consider blockade**

BIOMARKER

Activation marks the burden of injury without being the cause.

sC5b-9, Bb, C4d rising with vascular or tumor injury

→ **Risk-stratify. Do not treat the number**

BYSTANDER

Activated, but not causal for this kidney.

Sepsis · DIC · tumor lysis and necrosis · advanced malignancy

→ **Treat the real problem**

The question is never “is complement activated?” — in a sick cancer patient it almost always is. The question isn't whether complement is activated. It's whether it's doing the damage.”

One lab pattern, five different diseases

Thrombocytopenia, hemolysis and AKI in a cancer patient is a syndrome - not a diagnosis.

Platelets ↓ · LDH ↑ · schistocytes · AKI ± hypertension, proteinuria

TTP

ADAMTS13 < 10%;
PLASMIC score high;
kidney often spared

**Plasma exchange now.
This is the only clock
that runs in minutes.**

DIC / sepsis

PT, PTT, fibrinogen, D-
dimer abnormal; shock
physiology

Treat the source.
Support. Complement
blockade is not the
answer.

Cancer microangiopathy

Metastatic burden (up to
90%), marrow infiltration,
mucinous
adenocarcinoma,
leukoerythroblastic smear,
bone pain

**Treat the cancer, or
move to goals-of-care.
Plasma exchange is
generally futile.**

Drug-induced TMA

Gemcitabine, mitomycin
C, platinum,
VEGF/VEGFR inhibitors,
proteasome inhibitors,
ICIs

**Establish the exposure
timeline. Stop or modify
the drug. Biopsy when it
changes care.**

Complement-mediated

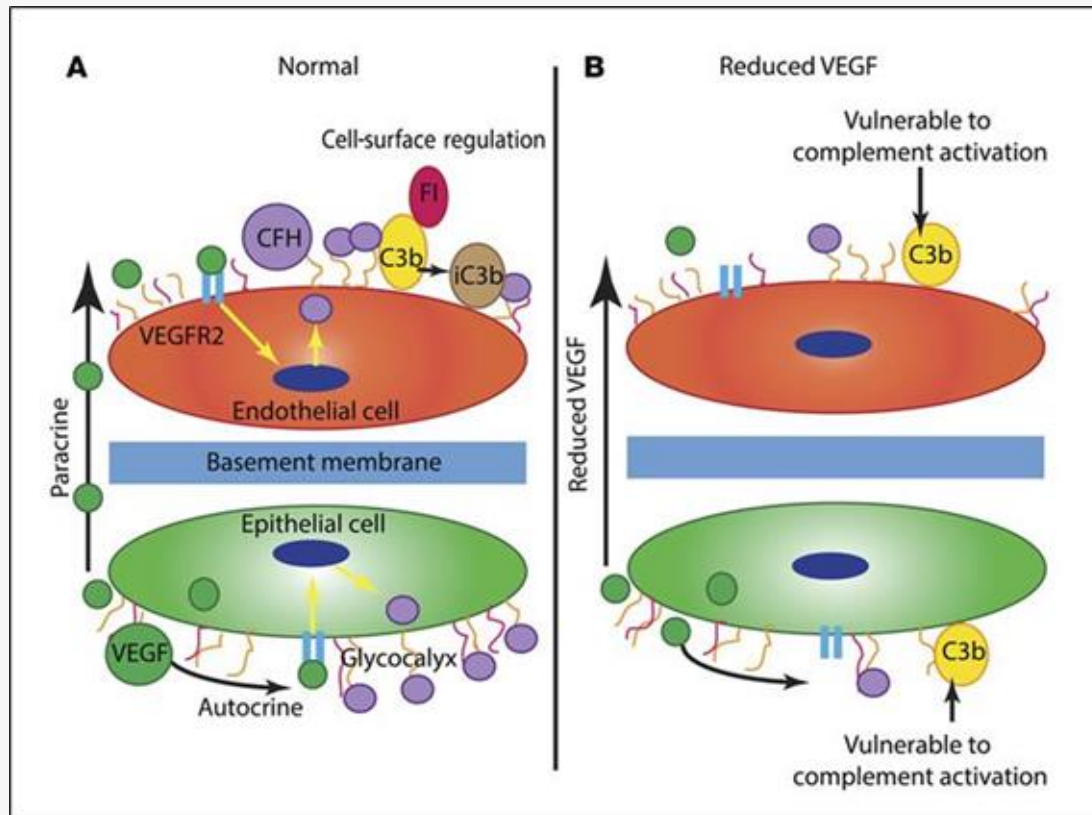
TMA persists after the
trigger is controlled;
susceptible host; low C3
with normal C4 in some;
family history

**This is the one where
complement blockade is
the treatment, not an
add-on.**

Draw the ADAMTS13 before plasma exchange. A normal result does not solve the case - it only removes the mimic

Anti-VEGF TMA is a complement lesion, not a complement indication

VEGF sustains local factor H. Remove VEGF and the glomerular endothelium loses its brake.



Left: podocyte- and RPE-derived VEGF sustains endothelial factor H. Right: with VEGF reduced, local regulation is lost and the surface becomes complement-vulnerable.

The experiment

VEGF induced factor H synthesis by glomerular endothelial cells. VEGF inhibition reduced factor H expression and increased C3d and C4d deposition in both kidney and eye. Cells from patients carrying CFH risk variants deposited more complement.

Why the eye matters here

The same VEGF–factor H axis operates at the choriocapillaris. It is why anti-VEGF nephrotoxicity and age-related macular degeneration share complement genetics.

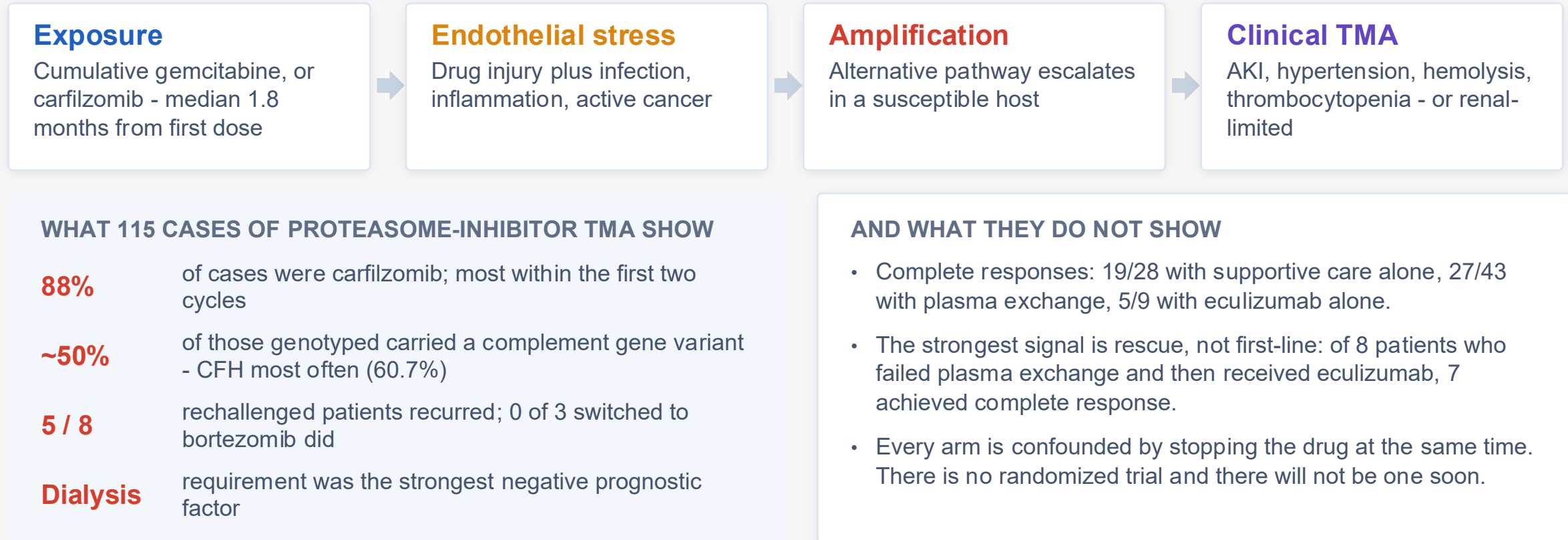
What to actually do

Hold or reduce the agent with the oncologist. Control blood pressure; RAAS blockade for proteinuria. Biopsy when the phenotype is severe, atypical, or when histology will change the oncology decision.

Complement blockade is not the default response to anti-VEGF TMA. Reserve it for severe, progressive, organ-threatening disease that persists after the drug is stopped.

Gemcitabine, proteasome inhibitors, and the amplifier phenotype

Real complement amplification, weak evidence: the best-characterized dataset is entirely observational.



Practical reading: stop the drug, exclude TTP and DIC, biopsy when feasible — and reserve complement blockade for TMA that is severe, progressive, or not settling after withdrawal.

TA-TMA: three hits, and an approved therapy since 2025

A complication of curative oncology, and the clearest place where complement blockade has arrived.

HIT 1 Susceptible host

Complement gene variants and polymorphisms; pre-existing endothelial injury

HIT 2 Conditioning

Total body irradiation and high-dose chemotherapy injure endothelium

HIT 3 The pile-on

GVHD, infection, calcineurin inhibitors and mTOR inhibitors, alloreactivity



Endothelial injury + complement amplification

Kidney, gut, CNS, lung - a multi-organ syndrome. Elevated sC5b-9, proteinuria ≥ 1 mg/mg, and hypertension mark high risk.

Narsoplimab-wuug (Yartemlea)

MASP-2 inhibitor — blocks the lectin pathway. FDA approved 23 December 2025 for adults and children ≥ 2 years with HSCT-associated TMA. 4 mg/kg (or 370 mg) IV weekly; median 8 doses.

61%

pivotal study
(n = 28)

67%

expanded access
pediatric (n = 6)

69%

expanded access
adult (n = 13)

TMA response = improvement in BOTH LDH and platelets, PLUS either improved organ function or transfusion independence. 100-day survival 73.4%.

Single-arm, open-label, small, composite endpoint. Hemorrhage 43%, viral infection 36%, neutropenia 36%. It does not replace early recognition, risk stratification, or supportive endothelial care.

A clone too small to treat can be large enough to destroy a kidney

Where onconeurology and complementology are the same specialty.

Plasma-cell or
B-cell clone



Monoclonal Ig
or light chain

Autoantibody-like activity

Against factor H, factor I, or the C3 convertase itself, including C3 nephritic factor

Immune complex / cryoglobulin

Complement fixation and deposition in the glomerulus

Direct endothelial injury

Paraprotein toxicity to the microvasculature

KIDNEY PHENOTYPES

C3 glomerulopathy · MPGN · immune-complex GN · cryoglobulinemic GN · thrombotic microangiopathy

Screen for a clone even when the M-spike is trivial. Serum and urine electrophoresis with immunofixation, free light chains, and a marrow when the kidney lesion is clone-shaped. The biopsy phenotype - C3-dominant, immune-complex, or TMA directs everything that follows.

2025: C3G IS NOW A TREATABLE DISEASE

- Iptacopan (factor B inhibitor) — approved 20 March 2025 for C3G in adults; APPEAR-C3G showed a 35.1% reduction in proteinuria versus placebo.
- Pegcetacoplan (C3 inhibitor) — approved 28 July 2025 for C3G and primary IC-MPGN in patients ≥ 12 years, including post-transplant recurrence; VALIANT showed a 68% proteinuria reduction at 26 weeks.

Clone-directed therapy is often the real complement drug. Complement blockade is adjunctive — for rapidly progressive disease, or while the clone-directed therapy takes effect.

The workup runs in parallel — the decision does not

Cancer patient, AKI or hemolysis or biopsy TMA: what to send, and when the answer is complement.

HOUR 0

- CBC with smear, LDH, haptoglobin, reticulocytes, direct Coombs
- ADAMTS13 — drawn before any plasma exchange
- PT, PTT, fibrinogen, D-dimer
- Blood pressure trend, urinalysis, UPCR, creatinine trajectory

SAME DAY

- Drug and transplant timeline — dose, cumulative exposure, days from insult
- Infection and sepsis evaluation
- SPEP, UPEP, immunofixation, serum free light chains
- C3 and C4

DAYS

- Kidney biopsy when it will change management
- sC5b-9, Bb, C4d, AH50 / CH50
- Factor H autoantibody, C3 nephritic factor
- Genetics: CFH, CFHR3-CFHR1 deletion, CD46, CFI, C3, CFB, THBD, DGKE

TREAT AS COMPLEMENT-MEDIATED

Severe or progressive organ injury · trajectory failing despite trigger control · biopsy supports TMA or complement-mediated GN · dominant alternatives addressed · you can state a causal hypothesis in one sentence

An abnormal complement test on its own · clear DIC or sepsis · renal-limited anti-VEGF lesion already improving after drug hold and BP control · advanced malignancy microangiopathy with no complement phenotype · no plan for how you would stop

If you do block terminal complement in an immunosuppressed cancer patient: meningococcal vaccination plus antibiotic prophylaxis, counselling about encapsulated organisms, and decided on day one the endpoint at which you will reassess or stop. Complement blockade without a stopping rule is not a treatment plan.

Four rules for cancer and complementology

1

Context decides

The same fragment kills a tumor cell in one patient, recruits MDSCs in another, and lyses glomerular endothelium in a third. Ask which cancer, which compartment, which cell made it.

2

Compartment matters

Plasma, membrane, tumor microenvironment and cytosol tell different stories. Our assays only see the first. A normal complement panel does not exclude tumor-cell complement biology.

3

Prognostic is not predictive

Bb, C4d, C1s, factor H and sC5b-9 are real signals. Not one of them yet selects a therapy. Anchor every biomarker to a phenotype, a timeline, and preferably a biopsy.

4

Name the role before the drug

Driver, amplifier, biomarker, or bystander. Treat triggers and clones first. Reserve complement blockade for high-confidence, organ-threatening, or approved indications — with a stopping rule.

Complement is a precision tool. Name the biology before you block it.