Contents

If You're Reading This

A patient's guide to combinatorial cancer immunotherapy

A reference for patients and families exploring immune-led treatment pathways

---

Before you begin

If you have found this document, you are probably going through something hard. You or someone you love has received a difficult cancer diagnosis. You are doing research — reading studies, asking questions, looking for paths your initial doctors may not have discussed. You are not asking for false hope. You are asking for clear information that respects your intelligence.

This document is written for that person.

It is **not a treatment plan, not a recommendation, and not medical advice.** It is a guide to a framework — a way of thinking about cancer treatment that takes seriously the immune system's role in fighting cancer, and that combines existing treatments in deliberate ways to engage that system fully.

The framework is **investigational.** Many of the individual components are established and FDA-approved, but the combinations are not validated by randomized trials. The framework's central claims have not been proven in the way a new drug is proven. They have been hypothesized, built from published evidence, structured in a way that could be tested, and applied in a small number of real cases — including, as the empirical anchor, one patient whose 15-year recurrence-free outcome after Stage IIA (pT2 pN0) high-grade BRCA1+ triple-negative invasive ductal carcinoma with metaplastic features was treated within the framework's principles.

Every important decision about your treatment should happen between you and a qualified oncologist who knows your specific situation. This document exists to help

you have a more informed conversation with that oncologist — not to replace them.

If after reading this you want to bring the framework to your oncologist, the technical documents (the framework paper, the clinical protocol, the decision-support tool) are referenced at the end. They are written for clinicians and contain the evidence base for everything described here.

---

1. What this framework is, in plain language

The body's immune system, in principle, can recognize and destroy cancer cells. The immune system does this routinely — small precancerous cell populations are eliminated all the time, without us noticing. What we call "cancer" is what happens when those mechanisms fail and abnormal cells multiply unchecked.

Modern oncology has spent most of the last 70 years developing treatments that attack cancer cells directly — chemotherapy that kills dividing cells, radiation that damages tumor DNA, targeted drugs that block specific cancer pathways. These treatments save lives. They also, in many cases, fail — because they do not address the underlying immune failure that allowed the cancer to grow in the first place.

The last fifteen years have seen the rise of **immunotherapy** — treatments that work by unblocking, training, or activating the immune system to fight cancer. Checkpoint inhibitors like pembrolizumab (Keytruda) and nivolumab (Opdivo) have transformed treatment for melanoma, some lung cancers, and a few other tumor types. Cancer vaccines, intratumoral therapies, and cytokines (IL-15 superagonists) are emerging.

The framework this guide describes is built around a specific observation: **immune-led cancer treatment usually works only when many immune mechanisms are engaged together, not just one.** The framework identifies seven characteristic ways the immune system fails against cancer (described below), and proposes that effective treatment must engage all seven — what it calls *combinatorial completeness*.

For most patients with advanced cancer, current standard treatment engages two or three of these seven modes well, leaves three or four unaddressed, and assumes that maximum-dose chemotherapy will compensate for the unaddressed gaps. The framework's central hypothesis is that closing the gaps — engaging all seven modes through combinations of validated components — produces qualitatively better outcomes than maximum-dose chemotherapy alone.

The framework also makes a specific argument about chemotherapy: in the framework's view, chemotherapy and radiation are best used not as the primary treatment, but as *immune triggers* — agents that release cancer antigens and create the conditions under which the immune system can attack. Used at the lowest effective dose, sequenced after immune priming, and supported by infrastructure that protects immune function during treatment, chemotherapy becomes a part of an immune-led strategy rather than the strategy itself.

One element of the framework deserves to be flagged here at the outset, because it is what most distinguishes this approach from generic combination immunotherapy: **sustained fever-range thermal stress at 39–40°C**. The body's normal fever

response is part of how the immune system fights infection — heat-shock proteins released by stressed cells act as immune adjuvants, dendritic cells traffic more efficiently to lymph nodes, and tumor cells (whose heat tolerance is lower than normal tissue's) are stressed and partially killed. William Coley's 19th-century bacterial vaccine worked partly because it reliably induced sustained high fevers. The modern framework preserves this principle: protocols that achieve sustained fever-range thermal stress — through whole-body hyperthermia equipment or through fever-titrated dosing of bacterial or synthetic immune activators — are predicted to produce qualitatively different responses than the same components administered without the fever component. This is why centers that practice combinatorial immunotherapy typically include whole-body hyperthermia as a core element rather than an optional adjunct, and it is one of the questions worth asking your oncologist about specifically (Section 8).

---

2. The seven failure modes — what your immune system needs to do

For the immune system to defeat cancer, seven things have to work. Effective treatment, the framework argues, must address all of them.

Mode 1 — Antigen presentation. The cancer must present recognizable molecular signatures (called antigens) that the immune system can identify as foreign. Some tumors do this well (those with high mutational burden, MSI-high tumors, BRCA-mutated tumors); others do this poorly (most pancreatic cancers, many breast cancers).

Mode 2 — T cell priming. Naive T cells must be activated against tumor antigens. This is what Coley's bacterial vaccine did in 1890s, what modern TLR agonists do (poly-ICLC, CpG, imiquimod), and what cancer vaccines do. When this fails, the tumor is "cold" — invisible to the immune system.

Mode 3 — Physical access. Activated T cells must reach the tumor. Dense scar-like tissue (stroma) around tumors blocks T cells; abnormal blood vessels prevent them from getting in. Bevacizumab and similar drugs target this barrier.

Mode 4 — Defeating exhaustion. T cells that reach the tumor often become exhausted — the cancer turns off their attack capability through PD-1 / PD-L1 signaling. Checkpoint inhibitors restore the function of exhausted T cells. This is what pembrolizumab does.

Mode 5 — Overcoming suppression. Tumors actively recruit suppressor cells (regulatory T cells, MDSCs) and create suppressive metabolic conditions (adenosine signaling, TGF-β). Low-dose metronomic chemotherapy and CD73 inhibitors target this.

Mode 6 — Persistence and memory. Anti-tumor T cells must persist long-term, not just respond initially. Without persistence, even strong initial responses fade and the cancer returns. IL-15 superagonists (like N-803) support persistence directly.

Mode 7 — Heterogeneity coverage. Tumors contain many different cancer cell clones. Treatments that target only one antigen allow the others to escape. Broad

immune responses, multi-antigen vaccines, and treatments that release diverse tumor antigens (radiation, certain forms of cell death) provide breadth.

In conventional treatment, most patients get Mode 4 (checkpoint inhibitor) and maybe Mode 1 (if the tumor happens to have good antigens) — but Modes 2, 3, 5, 6, and 7 are largely unaddressed. The framework argues this partial coverage is why immunotherapy works for some patients but not most.

---

3. The Coley lineage — and why "alternative" doesn't mean unscientific

The framework draws explicitly from a clinical tradition that predates modern oncology, founded by a surgeon whose credentials were as conventional as any in American medicine. William Bradley Coley (1862–1936) graduated from Yale College, took his medical degree from Harvard in 1888, interned at New York Hospital, and in 1892 — at age thirty — was appointed to the staff of the New York Cancer Hospital, the second institution in the world dedicated specifically to cancer treatment. That hospital, founded at 106th Street and Central Park West, was renamed General Memorial Hospital in 1898 under the influence of William Astor, later became Memorial Hospital, and in 1948 became what we now know as Memorial Sloan Kettering Cancer Center. Coley spent his entire professional career there. From 1915 until his retirement in 1933, he was head of the Bone Tumor Service — one of Memorial Hospital's principal clinical divisions, treating what was then the most refractory class of malignancies. He was, in his time, what we would now call a senior subspecialty chief at America's premier cancer institution.

Coley's encounter with cancer began with a single patient. In 1890, in his first year of private practice, he treated a seventeen-year-old named Elizabeth (Bessie) Dashiell who had developed a rapidly growing tumor in her hand. Despite amputation, the cancer spread and she died within months. Coley, struck by her case, went back to the hospital archives looking for sarcoma patients who had survived. He found one — a German immigrant named Fred Stein whose neck sarcoma had vanished after he developed erysipelas, a streptococcal skin infection. Coley tracked Stein down in Manhattan and confirmed that his cancer had not returned. From this single retrospective case, Coley formed the hypothesis that bacterial infection might be inducing the immune response that destroyed the tumor — a hypothesis he would spend the next four decades testing.

Between 1891 and 1936, Coley treated more than one thousand cancer patients with what came to be called Coley's Toxins — mixed bacterial preparations of killed *Streptococcus pyogenes* and *Serratia marcescens* that induced high fevers and sometimes produced striking tumor regressions. He wrote over 150 scientific papers. His colleagues included William Welch at Johns Hopkins, Harvey Cushing at Harvard, and the Mayo brothers. He held appointments as clinical professor of surgery (1909) and clinical professor of cancer research (1915) at Cornell University Medical School. By any conventional measure of his era, he was a distinguished member of the medical establishment.

His methods nevertheless fell out of favor. Several forces contributed. The bacte-

rial preparations were difficult to standardize — different manufactured batches produced different effects, and reliability was a recurrent problem. The rise of radiation therapy in the 1910s-1920s and chemotherapy in the 1940s offered more controllable interventions. And, importantly, Coley had a difficult relationship with James Ewing — the renowned pathologist who became Medical Director of Memorial Hospital and was therefore effectively Coley's institutional superior. Ewing was a champion of radiation therapy and skeptical of Coley's claims; their conflict shaped what research the hospital published and which methods received institutional support. By the 1940s, after Coley's death, his methods had largely been abandoned in mainstream oncology, surviving only in pockets of practice in Europe and the Americas.

After Coley's death in 1936, his daughter Helen Coley Nauts spent the next sixty-four years working to preserve and revive his methods. She founded the Cancer Research Institute — now one of the major funders of cancer immunotherapy research worldwide — and tracked down thousands of her father's case records to assess outcomes retrospectively. She worked until her death in 2000 at age 93. The Cancer Research Institute remains an active scientific organization, supporting checkpoint inhibitor research, vaccine research, and adoptive cell therapy — all descendants of the immunotherapeutic principle Coley introduced.

We now understand, retrospectively, what Coley was doing biologically. His bacterial vaccine engaged multiple immune receptors simultaneously — what we now call TLR2, TLR4, and TLR9 — the receptors that recognize bacterial molecular patterns. It induced sustained fever responses that released heat-shock proteins, activated innate immunity, and trafficked dendritic cells to lymph nodes. It produced broad immune activation across multiple modes at once. He was, without knowing it, doing combinatorial PAMP immunotherapy a century before either the concept or the molecular tools existed. The modern immunology of TLR signaling, dendritic cell biology, and innate-adaptive immune coordination — all of which post-date Coley's work by sixty to a hundred years — provide the mechanistic explanation for what Coley observed empirically.

The framework's modern Coley method preserves Coley's logic with modern molecular precision: poly-ICLC for TLR3 engagement, mistletoe or mixed bacterial vaccine preparations for multi-PAMP activation, intratumoral injection to provoke local immune response, whole-body fever-range hyperthermia for the sustained thermal stress component that Coley's fevers provided, all combined with the elements Coley's era could not access — checkpoint inhibitors (Mode 4) and IL-15 superagonists (Mode 6). The framework's argument is not that Coley was right about everything; it is that Coley's *empirical observations* identified a real biological phenomenon that modern science now has the tools to reproduce more reliably and to extend with components Coley could not have imagined.

A small number of clinical centers have continued working in this lineage throughout the modern era. The most prominent include CHIPSA Hospital in Tijuana, Klinik St. Georg in Bad Aibling, the Paracelsus Klinik in Lustmühle, several hyperthermia-focused centers in Japan, and a handful of integrative oncology programs at academic institutions. The quality of practice across these centers varies considerably — some maintain rigorous documentation and conservative claims, others do not. The framework does not endorse any specific center. It tries to extract the *principles* that the

best-practicing centers appear to be using, and to make those principles testable against the published evidence base.

There is a striking institutional irony in this history that bears mention. The framework's author once met an oncologist who had completed his medical training at Memorial Sloan Kettering Cancer Center — the institution that, as Memorial Hospital, employed William Coley for forty-one years and where he served as head of the Bone Tumor Service for eighteen of those years. The oncologist had never heard of Coley. He did not know that combinatorial immunotherapy had originated at his own training institution more than a century before the term "immunotherapy" existed in its modern form. This is not unusual. The contemporary teaching of oncology at major academic centers largely does not include Coley. His methods, his patients, his publications, and the institutional history of his work have been erased from the standard curriculum. A patient who today proposes a "Coley-inspired" treatment approach to an MSK-trained oncologist is, in most cases, proposing something the oncologist has never been taught about — even though it was developed in their own building. This is worth knowing if you find yourself talking with your oncologist about this framework and meeting a blank stare at the name. The unfamiliarity is not evidence that the history is fringe; it is evidence that the history was forgotten.

This matters because integrative oncology as a contemporary field also has reputational problems. There are practitioners who have done harm by advising patients to refuse conventional treatment that would have saved their lives. There are clinics that charge enormous sums for unproven treatments and produce poor outcomes. The framework's response to this is not to ignore the problem but to be explicit about it: the framework's components are mostly FDA-approved or investigational drugs being used in deliberate combinations, with explicit reference to the published evidence for each. Coley's own work — done at America's premier cancer hospital, peer-reviewed in the journals of his era, replicated across hundreds of cases over forty years — is not "alternative medicine." It is the unrecovered history of mainstream oncology. What is alternative is not the principle of combinatorial immunotherapy. What is alternative — temporarily, until the field catches up with itself — is the willingness to take that principle seriously.

---

4. Where the evidence comes from — and where the evidence ends

This is the section that matters most. Honest discussion of evidence is the difference between this framework and the marketing of unproven treatments.

Individual components are well-studied. Pembrolizumab, nivolumab, atezolizumab, durvalumab — all have large randomized trials and FDA approval. Olaparib and talazoparib (PARP inhibitors) have OlympiA-class evidence in BRCA-mutated cancers. Bevacizumab has decades of mCRC and other-indication data. N-803 has the QUILT-3.032 NEJM Evidence trial. Whole-body hyperthermia has German and Japanese clinical research dating back decades. Poly-ICLC has dozens of investigational trials.

Some combinations are studied. KEYNOTE-522 established pembrolizumab +

chemotherapy in TNBC. The autogene cevumeran trial (Rojas et al., Nature 2023) established personalized mRNA vaccines in pancreatic cancer. The Hammerich 2019 in-situ vaccination protocol in indolent lymphoma demonstrated abscopal responses from sequential Flt3L → radiation → poly-ICLC. The Tuli SBRT + durvalumab data in pancreatic cancer shows striking 1-year overall survival (80%) — though with important caveats about progression-free survival and small samples.

Most combinations the framework proposes have not been tested in randomized trials. The combinatorial-complete approach — six, eight, ten components engaged simultaneously across all seven failure modes — is investigational. The framework's central hypothesis (that combinatorial completeness produces qualitatively better outcomes than partial coverage) has not been proven by an RCT. It has been suggested by case-series experience at specific centers, by the historical Coley record, and by the biological logic of the seven-mode model. None of these constitute proof.

The case-series evidence is real but methodologically limited. CHIPSA Tijuana has 30+ years of documented cases, including patients with stage IV cancers who survived far longer than statistical expectation. Similar case series exist for hyperthermia centers in Germany and Japan. These records are not randomized trials. They are subject to selection bias (the patients who came to these centers were highly motivated and often otherwise healthy), survivorship bias (we hear about the survivors more than the non-survivors), and the absence of matched controls. The case series suggest the framework's predicted phenotype occurs — they do not establish how often it occurs or what fraction of patients benefit.

One specific empirical anchor. The framework's author's wife was diagnosed in 2011 with Stage IIA (pT2 pN0) high-grade BRCA1+ triple-negative invasive ductal carcinoma with foci of metaplastic transformation — a difficult-to-treat subtype generally resistant to standard anthracycline-based chemotherapy. She received a protocol in two phases. The intensive first phase was three weeks at CHIPSA Hospital in Tijuana: Coley toxins (mixed bacterial vaccine sourced from MBVax in Canada), autologous tumor antigen vaccine prepared from her biopsy, and **weekly whole-body fever-range hyperthermia at 39–40°C** sustained two to four hours per session. After returning home, the author continued home administration of the Coley toxins, on the dosing schedule established at CHIPSA, through the surgical recovery period and into the chemotherapy phase. In parallel, assay-guided low-dose cisplatin + gemcitabine — selected by ex-vivo chemosensitivity testing through the Wiesenthal Cancer Group, an unusual choice for TNBC in 2011 that has since become more accepted — was administered at reduced dose by a cooperative US oncologist. Bilateral mastectomy (therapeutic left, prophylactic right reflecting BRCA1+ status) was performed on April 5, 2011. Fifteen years later, she remains recurrence-free. Published 5-year overall survival for Stage IIA metaplastic TNBC ranges from approximately 50% to 70% across series — making the observed outcome favorable for this subtype. This is one patient. It establishes that the framework's predicted outcome occurs in reality. It does not establish that the framework will produce that outcome reproducibly.

What does this mean for you? It means that if you adopt elements of this framework, you are participating in something that has biological plausibility, published evidence for components, and clinical precedent at specific centers — but that has not been validated by randomized trials. You are making an informed choice under

uncertainty. The framework is not a guaranteed alternative to conventional treatment; it is a different way of thinking about treatment that, in the right circumstances and with the right components, *might* produce better outcomes than partial-mode immunotherapy or maximum-dose chemotherapy alone. It might also not.

---

5. When this framework might be relevant to you

The framework is not a recommendation for every cancer patient. For many cancers and many situations, standard of care is the right answer. The framework becomes more relevant in specific circumstances.

You may want to discuss this framework with your oncologist if:

- You have triple-negative breast cancer, pancreatic adenocarcinoma, MSS metastatic colorectal cancer, or another cancer where standard treatment has limited curative options
- You have BRCA1 or BRCA2 mutation status and want a framework-aligned approach to either treatment or risk reduction
- You have failed one or more standard treatments and your oncologist is discussing palliative options or clinical trials
- You cannot tolerate standard chemotherapy due to age, comorbidities, prior heavy chemo exposure, or organ dysfunction
- You have considered standard treatment and are inclined to refuse it, and you want a framework that's more rigorous than "refuse chemotherapy"
- You have oligometastatic disease (a small number of distant metastases) that's amenable to local therapy combined with systemic immunotherapy
- You are seeking sustained engagement over time rather than maximum-intensity short-term treatment
- You are otherwise healthy and a strong candidate for combination immunotherapy

The framework may be less relevant if:

- You have a curable early-stage cancer with well-established adjuvant protocols
- You have a tumor type with strong targeted-therapy options that produce dramatic responses (HER2-positive breast cancer with trastuzumab, EGFR-mutated lung cancer with osimertinib, BRAF-mutated melanoma with combination targeted therapy)
- You have MSI-high disease that responds dramatically to checkpoint inhibitor monotherapy
- You have a hematologic malignancy with established curative protocols (CAR-T-eligible diseases, certain leukemias and lymphomas with high-cure-rate chemotherapy)
- You have a very aggressive cancer requiring immediate, rapid cytoreduction where the framework's slower immune-led approach may not be appropriate
- You are too unwell to mount an immune response (severe immunosuppression, end-stage organ dysfunction)

These are not absolute rules. Your specific situation may have features that change the calculus. The point is that the framework is for *specific situations* — not for "any patient with cancer who wants something different from standard treatment."

---

6. The harder questions — and how to think about them

Some decisions are particularly difficult. The framework doesn't answer these for you, but it can give you a way to think about them.

"Should I refuse chemotherapy?"

The framework's answer is: probably not, but the chemotherapy you receive should be at the lowest effective dose, ideally guided by an ex-vivo chemosensitivity assay (some centers offer this; Weisenthal-type tests, for example), and sequenced after immune priming has begun. The framework's view is that chemotherapy is most useful as an *immune trigger* — releasing tumor antigens, killing some tumor cells, sensitizing others — not as the primary treatment. Used this way, lower doses with appropriate sequencing can be more effective than higher doses given outside the framework.

Refusing chemotherapy entirely is the framework's *chemo-free pathway*, which exists for patients who cannot tolerate it or refuse it. In that pathway, stereotactic radiation (SBRT) or local ablation (cryoablation, RFA) replaces chemotherapy's antigen-release function. The chemo-free pathway has weaker evidence than the chemo-included pathway. It is most defensible in patients who have specific contraindications to chemotherapy or who have already failed multiple lines of standard chemotherapy.

"Should I travel for treatment?"

Some framework-aligned centers are outside the United States. CHIPSA is in Tijuana, Klinik St. Georg in Germany, Paracelsus Klinik in Switzerland. Traveling for treatment is a significant decision with real costs (financial, family-disruption, logistical) and real risks (continuity of care, regulatory differences, distance from your home support system).

The framework doesn't recommend traveling unless your home clinical situation cannot accommodate the framework's components and you have specifically identified a center that can. If your home oncologist is open to off-label combinations and willing to access components through expanded-access applications, you may be able to implement framework principles locally. If not, traveling becomes more relevant. This is a decision to discuss with your oncologist and with center medical directors at the candidate destination.

"Should I do both?"

Many patients ask whether they can do standard treatment and the framework. The answer depends on what "both" means. Standard treatment plus the framework's supportive components (vitamin D, low-dose cyclophosphamide if cytopenias allow, integrative-oncology elements like exercise and nutritional optimization) is generally compatible. Standard treatment plus the framework's investigational components

(poly-ICLC, vaccines, IL-15 superagonist) usually requires either expanded-access approval or a clinical trial enrollment, and may require careful sequencing to avoid drug interactions.

The framework's chemotherapy-as-trigger principle can be integrated into standard treatment without "leaving" standard care — for instance, by accepting standard neoadjuvant chemotherapy but advocating for response-guided de-escalation based on early indicators, or by pursuing strong-responder de-escalation of the more myelosuppressive components when the early response justifies it.

"How do I find a center that can do this?"

Centers that have explicitly framework-aligned practice are limited. The most established are: CHIPSA Tijuana (Mexico), Klinik St. Georg (Bad Aibling, Germany), Paracelsus Klinik (Lustmühle, Switzerland), Hyperthermia centers in Japan (multiple), some integrative oncology programs in the United States (UCSF Osher Center, some academic programs).

More commonly, framework principles can be implemented at academic centers with strong investigational-medicine programs *if your oncologist is willing to engage with the framework*. The technical documents (the protocol, the framework paper) are designed for clinician review. If your oncologist reads them and is interested, your local academic center may be able to deliver framework-aligned care.

"What if my oncologist refuses to engage?"

This happens. Many oncologists, for reasonable professional reasons, will not engage with frameworks that have not been validated by randomized trials. Some will engage politely but won't change their recommendations. A few will engage genuinely.

The framework does not require your home oncologist's endorsement to apply. You can seek a second opinion (always reasonable in serious cancer cases) at a center that's more likely to engage. You can enroll in trials that test framework-aligned components individually (many such trials exist; ClinicalTrials.gov is the registry). You can travel to a center that already practices in the framework's tradition. You can also accept your oncologist's recommendations and pursue framework-compatible supportive elements (exercise, vitamin D, nutritional optimization, low-dose metronomic chemotherapy where appropriate) within standard care.

If your oncologist is unwilling to engage with the framework even after reviewing the documents, that's a meaningful signal — they may be right that the framework isn't appropriate for your specific situation, or they may simply be conservative. Either way, you have the right to seek other opinions.

---

7. How to bring this to your oncologist

If after reading this you want to discuss the framework with your oncologist, the way you do it matters.

Don't bring it as "this is what I want to do instead." That positions the conversation as an adversarial one — you against your oncologist — and most oncologists

will respond defensively. They are also probably correct that the framework is not a wholesale replacement for whatever they're recommending.

Bring it as "I've been reading about this approach. Can we discuss it?" This positions you as a thoughtful patient doing your own research, which is your role and your right. Your oncologist may have specific reasons to be skeptical that turn out to be correct. They may also have specific reasons to be more open than you'd expect.

Bring the documents, but don't expect them to read everything immediately. The framework paper is technical and long. The protocol document is even longer. The plain-language summary or this guide is the right starting point for the conversation. If your oncologist is interested, the technical documents are available.

Have specific questions ready. Vague questions ("what do you think of immunotherapy in general?") produce vague answers. Specific questions get specific responses. Some examples:

- "Based on my tumor's specific characteristics, which of the seven failure modes does the framework predict are most important for me?"
- "Which framework components are realistic to access in my situation? Which require investigational access, expanded-access applications, or trial enrollment?"
- "If we did frame my treatment as immune-led with chemotherapy as a trigger rather than the primary treatment, what would change about what you'd recommend?"
- "Are there academic centers near us that have explored combinatorial approaches in tumor types like mine?"
- "If I wanted to add specific elements (vitamin D supplementation, exercise prescription, hyperthermia consultations), what would you advise about each?"

Listen to the oncologist's concerns. They have spent their career treating cancer patients. They have seen patients pursue unconventional treatments and benefit; they have also seen patients pursue unconventional treatments and harm themselves by deferring treatments that would have helped. Their skepticism deserves a hearing. The framework does not require you to fight your oncologist; it offers a way to think about treatment that you and your oncologist can engage with together.

Be prepared for the conversation to be ongoing. Your oncologist may not have an immediate answer. They may want time to review the framework, consult with colleagues, or research specific components. This is fine. The framework is not a one-time decision; it's a way of thinking about treatment that develops over weeks and months.

---

8. Specific questions to ask

Here is a more focused list of questions worth asking your oncologist, organized by topic.

About your specific tumor:

- What biomarkers have been measured on my tumor? Specifically: tumor mutational burden, microsatellite instability status, PD-L1 expression, CD8+ T cell infiltration, FoxP3+ regulatory T cell density, and stromal density?
- What does my tumor's biomarker profile suggest about which immune failure modes are most active?
- Are there additional tests we could do (immune profiling, ctDNA, multi-IHC panels) that would tell us more about my immune status?

About standard treatment:

- What is the expected outcome of the standard treatment you're recommending — both the best case and the realistic median?
- What are the specific toxicities I should expect, and how do they affect quality of life during and after treatment?
- Is the chemotherapy dose you're planning the maximum tolerated dose, or could a lower dose be considered with closer response monitoring?
- Are there opportunities to de-escalate based on early response indicators (ctDNA, imaging)?

About framework-aligned components:

- Are any of the framework components accessible to me through trials, expanded-access applications, or off-label use within the institution?
- Specifically: poly-ICLC, N-803 (Anktiva), olaparib if I'm BRCA-mutated, mRNA neoantigen vaccine, intratumoral immunotherapy?
- **Is fever-range whole-body hyperthermia (39–40°C) available at your institution or by referral?** The framework treats sustained fever-range thermal stress as central, not optional. If WBH equipment isn't available, are there partner centers (radiation oncology departments with hyperthermia capability, integrative oncology centers) you would refer to?
- Are there integrative oncology services here or nearby — for hyperthermia, vitamin status, nutritional optimization, exercise prescription?

About second opinions and centers:

- Are there other centers with stronger investigational-medicine programs in my tumor type that I should consider for a second opinion?
- Are there specific clinical trials that combine multiple framework-aligned components that I should look at?
- Are there integrative oncology programs at academic centers (UCSF, Memorial Sloan Kettering, MD Anderson, Dana-Farber, others) you'd recommend I consult?

About the framework itself:

- Are there specific elements of this framework that you find unreasonable? Why?
- Are there specific elements that you find plausible and worth pursuing even within standard care?
- Could we, as a baseline, ensure my treatment respects the framework's general principles (immune-preservation, response-guided dose adjustment, sustained engagement) even if we don't adopt every component?

9. Hope, realism, and the long view

I want to end with something honest about hope.

Cancer treatment has changed dramatically in twenty years. Patients with metastatic melanoma in 2005 typically lived less than a year. Today, with combination immunotherapy, 40-50% of stage IV melanoma patients are alive at five years, with many achieving durable responses. Patients with chronic myeloid leukemia, lung cancer with specific mutations, and HER2-positive breast cancer have all seen similar transformations. People who would have died are alive today, and well.

This means several things at once.

It means that *something works*. The body's biology, when engaged correctly, can defeat cancer. The patients who survive metastatic melanoma in 2024 are alive because their immune systems were engaged. The framework's central premise — that immune engagement can be curative — has been demonstrated repeatedly in specific tumor types and specific patient populations. The question is whether the framework's combinatorial-complete extension of this premise applies to tumors and patients where current standard immunotherapy doesn't reach.

It means that *medical knowledge is still developing*. What was unconventional in 2005 is standard of care in 2024. Patients who pushed for immunotherapy in 2010 were sometimes told they were unreasonable; many of them are alive today specifically because they pushed. There is no reason to assume that everything important about cancer treatment is already known in 2026. The framework may be partially or wholly wrong. It may also turn out to capture something important that the field hasn't yet validated.

It means that *individual outcomes are not predictable*. Some patients respond extraordinarily to treatment that doesn't work for most. Some patients have unusual tumors. Some patients are simply lucky. The framework offers a way to think about treatment that maximizes the chance of being one of the responders. It does not guarantee response. Patients on the framework do progress. Patients on standard care do achieve durable remissions. Neither outcome is predetermined.

The empirical anchor of this framework — one patient, fifteen years recurrence-free after Stage IIA high-grade BRCA1+ triple-negative breast cancer with metaplastic features — is not a guarantee. It is a demonstration that the predicted phenotype occurs in reality. Other patients with similar diagnoses have died despite similar protocols. Other patients have survived on standard treatment. The framework's wager is not that combinatorial completeness always works, but that it works often enough, in specific situations, to be worth pursuing for patients who would otherwise face poor odds.

Hope and realism are not opposed. The most honest position is: the framework offers a defensible, biologically-grounded, evidence-based way of thinking about cancer treatment that, in specific situations, may produce better outcomes than current

standard of care. It is investigational. It is not magical. It requires careful implementation, qualified clinicians, real medical infrastructure, and clear-eyed acceptance of uncertainty. With those things, it is an option worth knowing about.

Whatever path you choose, you are not alone. You are part of a long lineage of patients who have looked at difficult diagnoses and asked whether there were paths beyond what they were initially offered. Some of those patients are alive today specifically because they asked. Some are not, despite their best efforts and the best efforts of their doctors. That is the honest reality of cancer in 2026.

I wish you the best in whatever you decide.

---

10. Where to find more

The technical foundation for this framework is published openly. All documents are available without charge on Zenodo (a CERN-hosted research repository).

For patients and family members: - *Plain-Language Illustrated Summary* — a more visual introduction to the framework - *This patient guide* (the document you're reading)

For clinicians: - *Neo-Coley v2 framework paper* — the structural argument for combinatorial PAMP immunotherapy with sustained fever-range thermal stress (Monteiro 2026, Zenodo) - *Combinatorial immunotherapy framework — Paper 3* — the seven-mode model in detail - *Trial designs — Paper 4* — proposed clinical trial structures - *Compassionate-use clinical protocol* — implementation document for receptive centers, including indication-specific protocols for TNBC, PDAC, MSS CRC, and the chemo-free pathway

For self-research: - *Combinatorial Completeness Engine* — an interactive web-based tool that lets a clinician (or a curious patient bringing their oncologist) assess a specific patient's mode-failure profile, build a candidate protocol from available components, and review safety considerations - ClinicalTrials.gov — the registry of all clinical trials currently enrolling. Searches for individual framework components ("poly-ICLC + checkpoint", "N-803", "intratumoral immunotherapy") will surface relevant trials - The published trials cited throughout (KEYNOTE-522, autogene cevumeran, Hammerich in-situ vaccination, MEDIOLA, the SBRT + durvalumab data, others) — all available through PubMed

The framework's author, Eric Monteiro, is an independent researcher. He does not practice medicine, does not operate a clinic, does not sell products, and does not endorse any specific center. The framework is published openly under permissive license; anyone is free to use it, build on it, criticize it, or improve it.

A final note

This document is for patients. It exists because some patients, facing serious cancers, will discover the framework on their own and need a guide that helps them think about

it responsibly. It does not exist to recruit patients to the framework. It does not exist to undermine your relationship with your oncologist. It does not exist to promise outcomes that the framework cannot reliably produce.

If reading this document has helped you ask better questions of your oncologist, it has done its job. If it has prompted you to research specific trials, specific centers, or specific framework components and bring that research into your treatment planning, it has done its job. If it has given you a more structured way to think about a treatment landscape that may have felt overwhelming, it has done its job.

If reading this document has prompted you to refuse standard treatment that your oncologist recommends, please stop and reconsider. The framework is not a recommendation to refuse standard care. It is a way of thinking about combining and sequencing care that, in the right circumstances, may produce better outcomes. The best version of using this framework involves your oncologist, qualified clinical infrastructure, careful implementation, and honest acknowledgment of uncertainty. Pursuing it outside that context — refusing chemotherapy without medical guidance, traveling to clinics without verification, taking unproven supplements as substitutes for real treatment — is likely to harm you.

Cancer is hard. You are doing your best. So is your medical team. So am I. So is the framework. Together, with care and honesty, we can do better than we currently do. That's the work.

Eric P. D. Monteiro is the author of the Neo-Coley v2 framework and related works. He is an independent researcher, not a medical professional. This document was prepared as a patient-facing companion to the framework's technical literature. It is provided without warranty, is not medical advice, and should not be interpreted as such. All clinical decisions should be made in consultation with qualified medical professionals who know your specific situation.

Document version 1.0 — May 2026.

Contact: eric@miacreativeagency.com · ORCID 0009-0003-6805-1381