Seven-Mode Combinatorial Immunotherapy: A Compassionate-Use Clinical Protocol Framework for Integrative Oncology Centers

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Contents

Front matter

Document type: Clinical protocol framework for compassionate-use implementation

Audience: Medical directors, treating oncologists, integrative oncology specialists, and clinical operations leads at institutions with established legal and ethical authority to administer investigational or off-label combination protocols outside the standard clinical-trial pathway. This includes (but is not limited to): U.S. centers operating under FDA Expanded Access or the federal Right to Try framework; European centers with country-specific compassionate-use approvals; Mexican integrative oncology hospitals operating under COFEPRIS oversight (such as CHIPSA, where this framework's foundational case was treated); and analogous centers in Switzerland, Germany, and other jurisdictions with established expanded-access pathways.

Status: This is a clinical protocol framework. It is intended for evaluation, adaptation, and selective adoption by qualified medical teams. It is not a substitute for clinical judgment, institutional ethics review, or compliance with the laws and regulations governing the implementing institution.

Relationship to companion research: This document is the clinical-implementation companion to two technical preprints by the same author:

- *Combinatorial completeness in cancer immunotherapy: a structural framework for addressing the seven failure modes of immune-mediated tumor control* (Monteiro 2026, Paper 3 of the series)

- *Combinatorial-complete immunotherapy protocols: three proposed trial designs testing the seven-mode framework in immunotherapy-refractory cancers* (Monteiro 2026, Paper 4 of the series)

The research papers propose randomized controlled trials. This document adapts the same framework for single-patient compassionate-use settings where the trial pathway is not available — typically because the patient's disease is advanced, treatment cannot wait, or the patient does not meet trial enrollment criteria, and where the institution holds the legal authority to administer combination investigational protocols on an individual basis.

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1. Purpose and scope

1.1 What this document is

This document translates the seven-mode framework for cancer immunotherapy from its research-trial form (Paper 4 of the companion series) into a clinical protocol framework usable in compassionate-use settings. The translation is necessary because the trial designs in Paper 4 are structured for randomized comparison across populations, while compassionate-use treatment addresses a different question — *what is the best multi-mode protocol available to offer this specific patient now*, given their disease state, the components actually accessible to the treating institution, and the patient's informed preferences.

The document provides:

- A regulatory and ethical orientation for institutions considering adoption
- A clinical-adaptation summary of the seven-mode framework
- A component inventory with realistic procurement guidance
- A general protocol template (universal architecture)
- Three indication-specific protocols (BRCA1/2-mutated TNBC; resectable or oligometastatic pancreatic cancer; microsatellite-stable metastatic colorectal cancer)
- Safety, monitoring, and adverse-event management guidance
- Documentation and outcomes-tracking recommendations
- An honest acknowledgment of limitations

1.2 What this document is not

- **It is not a substitute for clinical judgment.** Every treatment decision remains the treating physician's responsibility, including dose selection, sequencing, monitoring, and modification.
- **It is not a substitute for institutional ethics and regulatory review.** Implementing institutions are responsible for ensuring all protocol elements comply with the laws and regulations of their jurisdiction.
- **It is not a recipe.** The protocol framework presents structured options, not prescriptive commands. Component selection, sequencing, and dosing must be adapted to the patient and to the institution's available toolkit.
- **It is not validated by randomized controlled evidence.** The framework's central prediction — that combinatorial-complete protocols produce qualitatively better outcomes than partial combinations — is a structural hypothesis, supported by case-series experience and mechanistic reasoning but not yet by RCT-level evidence. This is the central reason such protocols belong, today, in compassionate-use contexts and proposed trials — not in standard-of-care recommendations.
- **It is not a description of an approved treatment.** Any patient considering treatment under such a protocol must give informed consent based on a full understanding that the combination is investigational.

1.3 Why this document exists

Two facts coexist. First, the seven-mode framework predicts that combinatorial-complete immunotherapy protocols will help patients whom single-agent or narrow-combination immunotherapy cannot help. Second, the randomized trials that would validate this prediction will take years to design, fund, enroll, complete, and analyze. In that interval, patients with the cancers the framework addresses are dying — many of them with disease trajectories the framework's components could plausibly alter.

Compassionate-use frameworks exist precisely to bridge this gap. They are not a workaround of the regulatory system; they are part of it. Every major regulatory jurisdiction has formal pathways for individual-patient access to investigational therapy outside the trial setting, with structured requirements for documentation, informed consent, monitoring, and institutional oversight. The pathways exist because the alternative — denying access to interventions that may help while waiting for definitive evidence — is not ethically tenable when the disease will not wait.

This document provides the framework adaptation, the component-level practical detail, and the safety and documentation structure to support qualified institutions in offering combinatorial-complete protocols where the regulatory pathway permits and the clinical situation justifies.

1.4 The framework's core thesis — four conditions, not seven

The seven-mode framework described in Paper 3 — antigen presentation, T-cell priming, physical access, exhaustion, suppression, persistence, and heterogeneity — is the

structural articulation of how immunotherapy can fail. It is not, by itself, the framework's thesis. The thesis — articulated most directly in the companion Neo-Coley v2 paper and operationalized throughout this document — is that durable Coley-type responses require *four conditions in combination*: **(1)** combinatorial PAMP activation across multiple innate immune sensors; **(2) sustained fever-range thermal stress at 39–40°C as the dosing endpoint**; **(3)** multi-month treatment duration with intermittent scheduling to avoid endotoxin tolerance; and **(4)** preservation of host immune function through controlled (not maximum-dose) cytoreductive therapy. The seven-mode model explains *why* the four conditions are necessary — each condition addresses specific modes — but the four conditions are the implementation requirement.

The fever-range thermal stress condition is the one most easily lost in clinical translation and the one whose loss most directly explains the failure of modern bacterial immunotherapy trials to reproduce Coley's historical response rates. Implementing clinicians using this document are asked to take it as a load-bearing requirement, not as an optional adjunct. The mechanistic case is developed in §13.5 and in the companion Neo-Coley v2 paper Section 4; the practical implementation guidance — whole-body hyperthermia equipment where available, fever-titrated PAMP dosing where it is not — is integrated throughout the indication-specific protocols in Sections 7, 8, and 9.

2. Regulatory and ethical framework

The protocol described in this document involves combinations of investigational and off-label use of immunotherapy components. Such combinations are not approved as a combination by any regulatory authority. Their administration outside an approved clinical trial requires an appropriate compassionate-use, expanded-access, or analogous regulatory framework in the implementing jurisdiction. This section summarizes the principal pathways. It is general orientation, not legal advice; institutional legal and regulatory counsel must be consulted for each specific case.

2.1 United States

FDA Expanded Access (Individual Patient IND): Allows individual patients with serious or life-threatening conditions to receive investigational drugs outside clinical trials. Requires (a) physician sponsorship via a single-patient IND application, (b) sponsor agreement to supply the investigational agent, (c) institutional review board (IRB) approval, and (d) informed consent. The pathway is well-established for individual investigational agents; combination requests require coordination across multiple sponsors when each component has a different manufacturer.

Right to Try Act (federal, 2018): Provides an alternative pathway for terminally ill patients to access investigational drugs that have passed Phase I trials, without requiring FDA approval or IRB review. The pathway has more limited applicability than Expanded Access (limited to terminally ill patients, limited to drugs past Phase I) and depends on the manufacturer's willingness to supply.

Off-label combination of approved agents: Where every component is FDA-approved for at least one indication, off-label combination by a treating physician with informed consent is generally legally permissible, though institutional policies and payer coverage vary. The seven-mode framework's component set is partly composed of FDA-approved agents (pembrolizumab, bevacizumab, ANKTIVA/N-803 in NMIBC, etc.) used off-label or in off-label combinations.

2.2 European Union

EMA compassionate use: EU member states implement compassionate-use programs under EMA-coordinated guidance. Specific implementation varies by country. Germany's individual healing attempt ("individueller Heilversuch"), France's autho-risation d'accès compassionnel, and Italy's uso compassionevole are established national pathways.

Named-patient supply: Most EU jurisdictions allow individual-patient supply of investigational or non-locally-approved agents where the treating physician documents medical necessity and obtains informed consent.

2.3 Mexico

COFEPRIS framework: Mexico's regulatory authority (Comisión Federal para la Protección contra Riesgos Sanitarios) governs investigational and combination therapy. Mexican integrative oncology centers operating under COFEPRIS authority (including CHIPSA Hospital, which provided the foundational case for this work in 2011) have established practice in combination integrative protocols including Coley toxins, autologous tumor vaccines, hyperthermia, low-dose chemotherapy, and conventional immunotherapy components.

For international patients seeking compassionate-use treatment at Mexican centers, both Mexican regulatory framework and the patient's home jurisdiction may apply. Institutional legal counsel should clarify implications.

2.4 Switzerland and Germany — integrative oncology centers

A network of integrative oncology centers in Switzerland (Paracelsus Klinik, Klinik St. Georg's affiliates), Germany (Klinik St. Georg Bad Aibling, several others), and elsewhere operates under each country's framework for integrative and complementary cancer therapy. These centers typically combine evidence-based components (chemotherapy, checkpoint inhibitors where applicable) with integrative components (whole-body hyperthermia, Coley toxin protocols, autologous vaccines, etc.). Many have decades of accumulated case-series experience in combination protocols.

2.5 Universal ethical requirements

Regardless of jurisdiction-specific regulatory pathway, four ethical requirements apply universally to compassionate-use treatment with the framework described here:

Informed consent. The patient (and, where appropriate, family) must be informed in writing and verbally that (a) the combination protocol is investigational, (b) the framework supporting it is structural and case-series–based, not RCT-validated, (c) all predicted benefits are hypotheses not established results, (d) the combination carries risks including the additive and potentially synergistic toxicity of multiple immunologically active agents, (e) alternatives including standard of care and clinical trial enrollment have been considered and discussed, and (f) the patient may withdraw at any time.

Institutional ethics review. Some form of institutional ethics committee, IRB, or equivalent review is required in all jurisdictions for combination investigational protocols. Even in jurisdictions where the regulatory pathway does not mandate it (e.g., the U.S. Right to Try Act does not require IRB review), institutional review remains the standard of care.

Clinical equipoise consideration. Before offering this protocol to a patient, the treating physician should consider whether the patient could be enrolled in a relevant clinical trial. Compassionate-use protocols are not a substitute for trial enrollment where trials are accessible and the patient is eligible. The protocol described here is appropriate primarily for patients who (a) are ineligible for relevant trials, (b) cannot access them geographically, or (c) cannot afford the time their disease trajectory allows.

Outcomes tracking. Patients treated under compassionate-use protocols should have their outcomes documented systematically. This is both an ethical obligation (the patient's experience contributes to the field's understanding) and a practical necessity (institutions adopting this framework should maintain records that allow them to refine the protocol over time and that support future submission to registries or publications).

3. The seven-mode framework — clinical adaptation

This section provides a concise clinical-orientation summary of the seven-mode framework. The full structural argument is in Paper 3 of the companion series. Treating physicians implementing this protocol should be familiar with Paper 3 or its equivalent literature.

3.1 The seven failure modes

Anti-tumor immune control depends on success at seven sequential biological functions. Cancer escape requires failure at one or more of these. Successful immunotherapy must restore function at each failed mode:

Mode	Function	Common failure pattern	Therapeutic restoration
1	Antigen presentation and immune visibility	HLA class I downregulation; antigen loss	mRNA / peptide neoantigen vaccines; autologous tumor lysate vaccines; immunogenic-cell-death chemotherapy
2	T cell priming via dendritic cell engagement	DC dysfunction; insufficient innate stimulation	Intratumoral TLR agonists (poly-ICLC, BCG); Flt3L; in situ vaccination
3	Physical access to the tumor microenvironment	Stromal exclusion; abnormal vasculature; CAF barriers	Anti-VEGF (bevacizumab); stromal modifiers; intratumoral injection (mechanical disruption + danger signaling)
4	T cell function preserved against exhaustion	PD-1/PD-L1, CTLA-4, LAG-3, TIM-3 axis activation	Checkpoint blockade (pembrolizumab, nivolumab, ipilimumab, others)
5	Active immune suppression neutralized	Treg expansion; MDSC recruitment; adenosine/TGF-β axis	CD73/A2A inhibitors; low-dose cyclophosphamide; chemotherapy-mediated MDSC depletion
6	T cell persistence and memory	Insufficient IL-2/IL-15; lack of long-lived memory	IL-15 superagonist (N-803/ANKTIVA); sustained vaccine dosing
7	Coverage of tumor heterogeneity and clonal escape	Subclonal escape; antigen-loss variants	Polyclonal (broad antigen) vaccines; immunogenic chemotherapy releasing diverse antigens

3.2 The combinatorial-completeness principle

The framework's central operational claim is that **engaging six or seven modes simultaneously can produce qualitatively different outcomes from engaging one, two, or three.** Each individual mode-engagement may show modest effect alone. The combination of all seven shifts the patient from a state where the immune system cannot mount a sustained anti-tumor response to one where it can.

This is the framework's bet, and it is the bet a compassionate-use implementation is making with the patient.

3.3 The modern Coley lineage

The framework has a direct historical antecedent. William Coley's bacterial vaccine, used between approximately 1891 and 1936 with documented case-series outcomes that compare favorably to contemporary single-agent immunotherapy in matched indications, engaged Modes 1, 2, 5, 6, and 7 strongly and Mode 3 partially — six of the seven modes — but engaged Mode 4 essentially not at all, because checkpoint biology was unknown until the 1990s. The framework's combinatorial protocols are, in this sense, Coley's strategy refined into precise molecular components and completed with the Mode 4 engagement his era could not provide.

For an institution like CHIPSA, where Coley toxin therapy has been administered continuously for decades, this lineage is direct: the framework formalizes and extends what such centers already do, integrating modern molecular descendants (intratumoral poly-ICLC, IL-15 superagonist, mRNA vaccines, checkpoint blockade) into the same broad-engagement strategy that the underlying clinical tradition has long pursued.

3.4 The cardinal sequencing and dosing principle

The single most consequential implementation principle, and the one most often gotten wrong in conventional combination practice, is the sequencing and dosing of chemotherapy relative to immune priming.

The principle, stated plainly: In the immunotherapy-refractory cancers this framework addresses, chemotherapy alone does not cure. Maximum-dose cytotoxic chemotherapy in stage IV TNBC, metastatic PDAC, and metastatic MSS CRC produces, on average, response without cure — patients respond, progress, and die from their disease. If the cure has to come from the immune response, then chemotherapy's role in this framework is to **trigger and amplify the immune response, not to maximize cytoreduction at the expense of immune capacity.** Chemotherapy is used to "crack open" tumor cells — releasing antigens and danger signals — so that the immune system can mount the curative response. Chemotherapy is the trigger; the immune system is the cure.

This reverses the conventional priority. Conventional practice treats immunotherapy as an add-on to maximum-dose chemotherapy. The framework treats chemotherapy as a calibrated immune-trigger within an immunotherapy-led protocol.

The biological reasoning:

- Activated, clonally expanding anti-tumor T cells are among the most rapidly dividing cells in the body during an immune response. Rapidly dividing cells are exactly what cytotoxic chemotherapy preferentially kills. Heavy myelosuppressive chemotherapy administered after immune priming can therefore destroy the very T cell population the priming was intended to generate.
- However, several chemotherapy agents (oxaliplatin, anthracyclines, taxanes, platinums to varying degrees) induce *immunogenic cell death*: tumor cells die in a manner that releases tumor antigens and danger signals which activate dendritic cells. At moderate or even reduced doses, these agents can serve

as the *trigger* for an immune response — provided the priming machinery (vaccines, intratumoral danger signals, checkpoint blockade) is already active when the chemotherapy is given.

- Assay-guided or response-guided chemotherapy dosing identifies the minimum effective dose for a given tumor, preserving immune competence while still producing the immunogenic cell death the protocol depends on.

The operational dose hierarchy. The framework specifies a clear order of preference for selecting chemotherapy dose:

1. **First choice — assay-guided dosing.** Where fresh tumor tissue can be obtained and a chemosensitivity assay (e.g., Weisenthal-type ex-vivo testing through the Weisenthal Cancer Group, or other validated chemosensitivity testing) is available, the assay identifies the lowest effective dose of each agent for the specific tumor. This is the empirical anchor of the framework — it is what the foundational 2011 case used (Section 13.4) — and where institutional infrastructure permits, it is the preferred starting point.

2. **Second choice — response-guided dosing with reduced starting dose.** Where assay-guided dosing is not available, the framework's recommendation is to start at a reduced dose (typically 60–80% of standard) and escalate based on early response indicators: ctDNA clearance, radiographic response after 2–3 cycles, and clinical/tolerability response. If the patient is responding strongly, dose escalation is unnecessary — the goal has been achieved. If response is suboptimal after 2–3 cycles, escalate toward standard dose.

3. **Third choice — standard doses with close monitoring and willingness to de-escalate.** Where neither assay nor reduced-dose-start is feasible (urgent disease, institutional constraints, patient preference for established standard), use standard published doses but with close ctDNA and radiographic monitoring, and explicit willingness to de-escalate on strong response signals. The conventional "complete the full course at full dose regardless of response" approach is **not** the framework's recommendation.

Practical implications for the protocol:

1. Immune-priming components (intratumoral TLR agonist, vaccine, checkpoint blockade) begin first — before cytoreductive chemotherapy where the clinical situation permits — not added later as an afterthought.
2. Where a choice of chemotherapy agent exists, immunogenic and less myelosuppressive agents (platinums, taxanes, oxaliplatin) are preferred over maximally myelosuppressive regimens.
3. Where intensely myelosuppressive chemotherapy is judged necessary, immune components are sequenced so the primed response is established before the myelosuppressive phase and supported through it by Mode 6 (IL-15 persistence) agents.
4. The dose hierarchy above (assay first, then reduced + escalation, then standard) is applied to chemotherapy selection in every indication. The indication-specific protocols in Sections 7–9 instantiate this hierarchy.

This principle reflects empirical experience — including the foundational case dis-

cussed in Section 13.4 — as well as the mechanistic biology. It is the operational difference between adding immunotherapy to chemotherapy (the conventional approach, which often fails because the chemotherapy destroys the immunity) and using chemotherapy to support immunotherapy (the framework's approach).

4. Patient assessment and selection

4.1 The compassionate-use decision

Before offering a combinatorial-complete protocol to any patient, the treating team should work through a structured decision sequence:

1. **Is standard-of-care therapy appropriate and acceptable to the patient?** Compassionate-use protocols are not a first-line alternative for patients with potentially curable disease who can be treated with established protocols.
2. **Is the patient eligible for a relevant clinical trial, geographically and clinically?** If yes, trial enrollment is generally preferred over compassionate-use treatment, because trials generate the evidence needed to bring effective protocols to all patients.
3. **Does the patient's disease trajectory permit the time a trial requires?** Patients with aggressive disease and short time horizons may not be able to wait through trial enrollment.
4. **Does the patient understand and accept the investigational nature of the protocol and the absence of RCT-level evidence?** Informed consent is the threshold, not an afterthought.
5. **Is the institution's component toolkit adequate to deliver a meaningfully combinatorial protocol?** A clinic that can deliver, for example, only one or two of the framework's component categories may not be able to offer a protocol that the framework's logic supports.

A "yes" at each step indicates the patient is an appropriate candidate. A "no" at any step requires the team to revisit the recommendation.

4.2 Performance status and physiologic eligibility

Multi-agent immunotherapy combinations are demanding. Patients should be physiologically able to tolerate the combined toxicity. Suggested thresholds (to be adapted to clinical context):

- **ECOG performance status:** 0–2 generally appropriate. ECOG 3 requires very careful consideration; ECOG 4 generally inappropriate except for highly selected end-of-life palliative settings where benefits and risks have been explicitly discussed.
- **Major organ function:** Adequate hepatic, renal, cardiac, and bone marrow function. Specific thresholds depend on which chemotherapy and which immunotherapy components are planned. Standard pre-chemotherapy and pre-immunotherapy eligibility thresholds apply.
- **Active autoimmune disease:** Active or recent-onset autoimmune disease requiring systemic immunosuppression is generally a contraindication to check-

point blockade and IL-15 superagonist. Such patients require careful individual risk-benefit assessment and may need modified protocols.
- **Active infection:** Untreated active infection is a contraindication.
- **Pregnancy:** A contraindication for most components; reliable contraception is required for patients of reproductive potential.
- **Brain metastases:** Untreated symptomatic brain metastases are generally a contraindication; treated, asymptomatic, stable brain metastases require individual assessment.

4.3 Disease-state appropriateness

The framework targets specific disease states where multiple immune failure modes are operative and where the framework predicts qualitative benefit. Appropriate disease states (full detail in Sections 8–10):

- BRCA1/2-mutated triple-negative breast cancer — neoadjuvant or metastatic
- Pancreatic ductal adenocarcinoma — resectable, borderline-resectable, or oligometastatic
- Microsatellite-stable metastatic colorectal cancer — first-line or after progression on standard therapy

The framework's reasoning extends in principle to other tumor types where similar multi-mode failure patterns operate, including (with appropriate clinical judgment) checkpoint-refractory melanoma, certain ovarian cancers, and some sarcomas. This document does not specify protocols for those indications; treating teams considering extension should ground their decisions in the underlying framework (Paper 3) and recent literature.

4.4 Patient-specific factors affecting protocol modification

Beyond eligibility, several patient-specific factors should inform protocol customization:

- **Genetic context:** BRCA1/2 status, HRD status, TMB, MSI status, HLA type. Where available, these inform component selection (e.g., BRCA1/2 mutations favor platinum-based chemotherapy as the immunogenic trigger; high TMB increases the likely benefit of neoantigen-targeted approaches).
- **Tumor accessibility:** Whether tumors are accessible for intratumoral injection (cutaneous, superficial nodal, liver metastases with interventional radiology) determines whether Mode 2 intratumoral priming is feasible.
- **Tumor microenvironment data:** Where pre-treatment biopsies are obtained, immunohistochemistry for CD8, FoxP3, PD-L1, stromal density, etc., can inform which modes are most likely to be limiting in this specific tumor.
- **Prior therapy effects:** Recent chemotherapy may have produced lymphopenia that needs to recover before immune priming; prior immune-related adverse events on checkpoint blockade increase risk of recurrence.
- **Patient resources and access:** The full protocol assumes the patient can access the institutional setting for the duration of treatment. Logistic feasibility is part of the assessment.

5. Component inventory — function, sourcing, and dosing

This section catalogs the framework's component categories. For each: what it does (which modes), regulatory status as of preparation, principal sourcing pathways, published dose ranges, and notes on alternatives where the primary component is unavailable.

Dose verification requirement: Dose ranges cited in this section are based on published trial protocols current at the time of document preparation. Drug approvals, dosing recommendations, formulation availability, and combination-safety data continue to evolve. **Every specific dose used in implementing this protocol should be independently verified by the treating team against the most recent published trial protocols, current package inserts, and institutional pharmacy and therapeutics review.** This document is a framework reference; it is not a doses-of-record. Final dose selection in any individual patient remains the responsibility of the treating physician.

5.1 Intratumoral TLR agonist — the modern Coley component

Function: Mode 2 (innate immune activation, dendritic cell engagement) with effects on Mode 3 (stromal/microenvironmental disruption via local inflammation) and Mode 5 (transient reversal of local suppression).

Principal component: Poly-ICLC (Hiltonol). Polyinosinic-polycytidylic acid stabilized with poly-L-lysine and carboxymethylcellulose. TLR3 agonist.

- **Status:** Investigational. Available from Oncovir, Inc. (Washington, DC) under expanded-access mechanisms in multiple jurisdictions. Extensive safety data across multiple Phase I and II trials.
- **Published dosing — canonical intensive priming schedule:** The most extensively published intratumoral poly-ICLC schedule (used by Salazar, Hammerich, Kalinski, and colleagues across multiple Phase I and II trials) is **1 mg intratumoral three times weekly for 2 weeks (priming phase)**, followed by **intramuscular booster injections biweekly for 7 weeks**, with a 1-week rest period before any subsequent cycle. The Salazar/Mount Sinai durvalumab + tremelimumab combination protocol (NCT02643303) administers poly-ICLC on Days 1, 3, 5, 8, 10, and 15 of cycle 1, then IM on Days 17, 22, 24, then IM twice weekly during cycle 2, then twice in cycle 3. The Hammerich 2019 in-situ vaccination protocol for indolent NHL uses a sequenced strategy beginning with Flt3L (CDX-301) for dendritic-cell recruitment, followed by low-dose local radiation (2 Gy × 2 fractions) for antigen release, followed by intratumoral poly-ICLC for DC activation — implementing teams targeting the Hammerich abscopal-response result should reference that paper directly.
- **Adaptation for this framework:** for compassionate-use implementation where the canonical intensive schedule is operationally feasible, it is preferred. Where institutional capacity limits the injection frequency, a less-intensive schedule (1 mg twice in week 1, then weekly through Phase 1) is a reasonable but unstudied adaptation, with the trade-off that the immune-priming intensity is reduced. Dose is adjustable based on lesion size and clinical context. Local injection-site

reactions and transient febrile responses are expected and represent the desired pharmacodynamic effect — not adverse events to suppress.
- **Administration:** Direct intratumoral injection. For deep-seated lesions, image-guided injection by interventional radiology. For superficial lesions, direct injection by the treating oncologist.

Historical/alternative component: Coley's mixed bacterial vaccine (MBV / "Coley fluid"). - **Status:** No longer in routine production. Historical MBVax product was discontinued. Some integrative centers maintain access to investigationally-produced preparations. CHIPSA has a documented history of MBV administration. - **Dosing:** Historical Coley protocols varied widely. The standard pattern was escalating subcutaneous or intratumoral injections every 2–3 days for several months, with target febrile response. Modern integrative-center practice varies. - **Note:** MBV provides similar Mode 2 / 3 / 5 engagement as poly-ICLC but through broader PAMP activation. The trade-off is less precise dose-response and broader inflammatory response. Where both poly-ICLC and MBV are available, poly-ICLC's defined molecular profile and dose-response are generally preferred for protocol consistency.

Alternative component: Intravesical BCG (for bladder cancer indications only). Established and approved for non-muscle-invasive bladder cancer. Not directly relevant to the three indications detailed in this document but mentioned as an example of the same component category.

5.2 Personalized neoantigen vaccine

Function: Modes 1 (antigen presentation), 2 (DC engagement when adjuvanted appropriately), 6 (sustained antigen exposure), 7 (polyclonal coverage when multiple neoantigens included).

Principal component: Individualized mRNA neoantigen vaccine (autogene cevumeran-equivalent or analogous). - **Status:** Investigational. Production requires patient-specific tumor sequencing, neoantigen prediction, and manufacturing — typically 6–10 weeks. Manufacturing capacity is currently limited largely to clinical trial settings (BioNTech / Genentech for autogene cevumeran; Moderna for mRNA-4157/V940). - **Access pathway:** For most institutions, this component is currently accessible only through clinical trial enrollment. Compassionate-use access to individualized mRNA vaccines is rare but increasing as manufacturing scales. Institutions should track sponsor compassionate-use policies.

Alternative component: Autologous tumor lysate dendritic cell vaccine. - **Status:** Available at multiple integrative oncology centers, particularly in Germany (Klinik St. Georg and others), Switzerland (Paracelsus Klinik), and Mexico (CHIPSA, where this was used in the foundational case). Production typically requires fresh tumor tissue or peripheral blood mononuclear cells, with DC differentiation in vitro, antigen loading from tumor lysate, and reinfusion. - **Dosing:** Variable by center; typical protocols include 4–6 priming doses subcutaneously, weekly to biweekly, with possible maintenance doses. - **Trade-off:** Less precisely defined than mRNA neoantigen vaccines but available now in established practice; covers a broader range of tumor antigens (whole tumor lysate) but with less targeting precision.

Alternative component: Peptide cocktail vaccines (off-the-shelf shared antigen targets). Available for some tumor types from various sources. Generally less personalized but more readily available.

5.3 Checkpoint inhibitor

Function: Mode 4 (T cell exhaustion blockade).

Principal components:

- **Pembrolizumab (Keytruda, Merck):** anti-PD-1. FDA/EMA-approved for multiple indications. Off-label combination with other immunotherapy components is generally permissible with informed consent. Standard dose: 200 mg IV every 3 weeks or 400 mg every 6 weeks.
- **Nivolumab (Opdivo, BMS):** anti-PD-1. Similar profile to pembrolizumab. Standard dose: 240 mg every 2 weeks or 480 mg every 4 weeks. In combination with ipilimumab (CheckMate-style regimen), nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for 4 doses, then nivolumab maintenance.
- **Atezolizumab (Tecentriq, Genentech):** anti-PD-L1. Standard dose: 1200 mg IV every 3 weeks.
- **Ipilimumab (Yervoy, BMS):** anti-CTLA-4. Used in combination with anti-PD-1 in melanoma and other settings; higher toxicity than anti-PD-1 monotherapy.

All four are commercially available. Selection depends on indication, prior therapy, patient factors, and institutional formulary. For most indications in this protocol, anti-PD-1 monotherapy (pembrolizumab or nivolumab) is sufficient unless evidence indicates that dual checkpoint blockade is preferred.

5.4 IL-15 superagonist — the modern persistence component

Function: Mode 6 (memory T cell support, sustained immune engagement). Also synergizes with Modes 4 (NK cell activation) and 2 (DC support).

Principal component: N-803 / Anktiva (nogapendekin alfa inbakicept-pmln; ImmunityBio). - **Status:** FDA-approved (April 2024) for BCG-unresponsive non-muscle-invasive bladder cancer with CIS. Off-label use in other indications. - **Published dosing (from QUILT-3.032 / Chamie et al., *NEJM Evidence* 2023):** 400 µg intravesical (bladder indication; FDA-approved schedule with TICE BCG). **For systemic combination use** with checkpoint inhibitors, published combination experience across the QUILT-3.055 program and related trials uses **approximately 6–20 µg/kg subcutaneously every 2–3 weeks**, with **15 µg/kg every 3 weeks** being the dose used in the QUILT-3.055 NSCLC checkpoint-acquired-resistance cohort that produced the most informative combination signal to date. Lower doses (1–6 µg/kg) have been tested in early dose-escalation phases but appear less clinically active. For implementations in this framework, a starting dose of **6–10 µg/kg every 2 weeks** with escalation toward 15 µg/kg every 3 weeks based on tolerance is a reasonable approach, but treating teams should refer to the most current published trial protocols and adjust for patient-specific tolerance. - **Access:** Commercially available in the US. International availability is more limited but expanding.

Alternative component: ALT-803 (earlier formulation) or other IL-15-based agents. Investigational; access varies.

5.5 Stromal-modifying agent

Function: Mode 3 (physical access; reduction of stromal exclusion).

Principal components:

- **Bevacizumab (Avastin, Genentech/Roche):** anti-VEGF monoclonal antibody. FDA/EMA-approved for multiple indications including metastatic colorectal cancer (standard with FOLFOX backbone), recurrent ovarian cancer, glioblastoma, others. Vascular normalization improves T cell access to tumors. Standard dose: 5–15 mg/kg every 2–3 weeks depending on indication.
- **Losartan or other angiotensin-system inhibitors:** Evidence for stromal modification in pancreatic cancer through reduction of pancreatic stellate cell activity. Generally well-tolerated; off-label for cancer-related stromal modification.
- **FAK inhibitors (defactinib, etc.):** Focal adhesion kinase inhibition reduces stromal density. Investigational status; limited compassionate access.
- **Hyaluronidase (PEGPH20, etc.):** Targeted stromal degradation in pancreatic cancer. Investigational; access varies.

5.6 CD73 / adenosine axis inhibitor

Function: Mode 5 (suppression reversal; adenosine-mediated immunosuppression is a major Mode 5 mechanism).

Principal components:

- **Oleclumab (MEDI9447, AstraZeneca):** anti-CD73 monoclonal antibody. Investigational. Phase II data published; access via clinical trials or expanded access requests.
- **A2A receptor antagonists (ciforadenant, etrumadenant, others):** Block adenosine signaling. Investigational.
- **Low-dose cyclophosphamide as Treg-depleting alternative:** Where CD73 inhibitors are unavailable, metronomic low-dose cyclophosphamide (50 mg orally daily, or 100 mg every other day) has documented Treg-depleting effects and may provide partial Mode 5 engagement. Established and inexpensive.

5.7 Whole-body or local hyperthermia

Function: Supports Modes 1 (MHC upregulation), 2 (DC activation), 3 (vascular changes, T cell trafficking), and produces synergy with chemotherapy and radiation when sequenced appropriately.

Principal component: Fever-range whole-body hyperthermia. - **Status:** Available at numerous integrative oncology centers worldwide. Equipment includes infrared-A devices (heckel, others), water-jacketed systems, and others. CHIPSA, the European integrative centers (Klinik St. Georg, Paracelsus Klinik, others), and several U.S. centers have established hyperthermia practice. - **Dosing:** Target core

body temperature 39.0–40.5°C for 2–6 hours, weekly or biweekly during active treatment phase. Specific protocols vary by center. - **Local/regional hyperthermia:** For specific tumor sites; uses focused devices.

5.8 Immunogenic chemotherapy at controlled dose

Function: Modes 1 (antigen release through immunogenic cell death) and 7 (broad antigen coverage). Also provides direct cytoreduction.

Principal components for the indications in this protocol:

- **TNBC:** Carboplatin + paclitaxel (immunogenic, less myelosuppressive than anthracyclines); doxorubicin/cyclophosphamide as a later phase if needed.
- **PDAC:** mFOLFIRINOX (oxaliplatin highly immunogenic); gemcitabine + nab-paclitaxel as alternative.
- **MSS CRC:** FOLFOX (oxaliplatin) ± bevacizumab; FOLFIRI as alternative.

Dose-selection principle (framework default — Path A). Chemotherapy in this framework is the immune trigger, not the cure. Apply the dose hierarchy from Section 3.4 in every indication:

1. **First choice — assay-guided dosing.** Where fresh tumor tissue can be obtained and chemosensitivity testing (Weisenthal-type ex-vivo assays, ChemoFx, or other validated assays) is feasible, the assay identifies the lowest effective dose for the specific patient's tumor. This is the framework's preferred starting point.
2. **Second choice — reduced starting dose with response-guided escalation.** Where assay guidance is unavailable, start at approximately 70–80% of standard published doses with ctDNA, tumor-marker, and imaging reassessment at cycles 2–3. Continue at reduced dose if responding; escalate toward standard doses only if response is suboptimal.
3. **Third choice — standard published doses with active monitoring and willingness to de-escalate.** Reserved for cases where rapid cytoreduction is the priority. Even then, the framework does not endorse fixed full-course full-dose chemotherapy regardless of response — early de-escalation on strong response is the expected behavior, not the exception.

The framework's prior is that combinatorial-complete immunotherapy plus moderate-dose immunogenic chemotherapy can produce qualitatively better outcomes than partial-mode immunotherapy plus maximum-dose chemotherapy. This is the framework's testable hypothesis, supported by the foundational case (Section 13.4), the autogene cevumeran result, and the framework's structural logic. Implementing teams should be prepared to honor it operationally.

5.9 Component availability summary table

Component category	Principal agent	Status	Realistic access
Intratumoral TLR agonist	Poly-ICLC (Hiltonol)	Investigational	Oncovir compassionate access

Component category	Principal agent	Status	Realistic access
Personalized vaccine (mRNA)	Autogene cevumeran	Investigational	Currently trial-limited
Personalized vaccine (DC)	Autologous DC vaccine	Established practice (integrative centers)	Available at qualified centers
Checkpoint inhibitor	Pembrolizumab, others	Approved	Commercially available
IL-15 superagonist	N-803 (Anktiva)	Approved (NMIBC); off-label other	Commercially available US
Stromal-modifying	Bevacizumab	Approved	Commercially available
Stromal-modifying	Losartan	Approved (cardiovascular)	Off-label cancer use
CD73 inhibitor	Oleclumab	Investigational	Trials or expanded access
Treg-depletion alternative	Low-dose cyclophosphamide	Approved	Commercially available
Hyperthermia	Whole-body equipment	Device	Available at qualified centers
Immunogenic chemo	Various (above)	Approved	Commercially available

This availability landscape is the practical reality with which compassionate-use implementations must work. Few institutions can deliver every component on the framework's full menu. The general protocol template (Section 6) is designed to be implementable in graded fashion, with priority modes addressed first and additional modes engaged as resources permit.

6. General protocol template — universal architecture

This template applies to every indication. The indication-specific sections (7, 8, 9) instantiate it with the components and timing appropriate to each cancer type.

6.1 The five-phase architecture

The protocol unfolds in five phases, each with a defined purpose:

Phase	Duration	Purpose	Principal components active
0. Preparation	2–4 weeks	Workup, baseline assessment, vaccine manufacturing initiation, ethics/consent	Diagnostic only
1. Immune priming	2–4 weeks	Establish anti-tumor immunity *before* cytoreduction	Intratumoral TLR agonist, checkpoint inhibitor, vaccine (when manufactured), hyperthermia
2. Immunogenic trigger	8–16 weeks	Cytoreduction via immunogenic-dose chemotherapy *while immunity is active*	Adds immunogenic chemotherapy at controlled doses; continues priming components
3. Sustained engagement	8–24 weeks	Protect and amplify the primed response through and beyond cytoreduction	IL-15 superagonist support; continued checkpoint blockade; vaccine maintenance; stromal/suppression modifiers
4. Surveillance / maintenance	12+ months	Sustained immune support; early relapse detection	Maintenance checkpoint, IL-15, vaccine; periodic ctDNA and imaging

This sequencing inverts the conventional order. Conventional combination practice often runs full-dose chemotherapy first and adds immunotherapy afterward. The framework's order is the opposite: immunity first, chemotherapy as trigger second, sustained immune protection third.

6.2 Phase 0 — Preparation

Workup and baseline assessment (typical):

- Histologic confirmation of diagnosis and complete molecular characterization (HER2, hormone receptor status for breast; BRCA1/2; HRD; MSI; TMB; PD-L1;

other markers as indicated by tumor type)
- Imaging: CT chest/abdomen/pelvis, MRI as indicated, bone scan as indicated, PET-CT where useful
- Comprehensive laboratory: CBC with differential, comprehensive metabolic panel, LDH, magnesium, hepatitis screen, HIV, TSH, cortisol, lipase, troponin, NT-proBNP (cardiac monitoring will be needed for checkpoint+IL-15 combinations)
- Cardiac assessment: ECG, echocardiogram (LVEF baseline) — especially with planned anthracycline or IL-15 use
- Pulmonary function tests where indicated (pneumonitis risk with checkpoint blockade)
- Where feasible: pre-treatment tumor biopsy for immune profiling (CD8, FoxP3, PD-L1 IHC, stromal characterization) and for vaccine manufacturing input
- Where feasible: baseline ctDNA assessment for downstream response monitoring
- Where feasible: chemosensitivity assay on fresh tumor tissue
- HLA typing where mRNA neoantigen vaccine is planned

Documentation and consent:

- Comprehensive informed consent document covering all planned components, the investigational nature of the combination, the absence of RCT-level evidence, the framework's hypotheses as hypotheses, and alternatives including standard of care and clinical trial enrollment
- Institutional ethics/IRB documentation as required by jurisdiction
- Compassionate-use applications for components requiring them (e.g., poly-ICLC expanded access)
- Treatment plan document signed by treating physician and patient
- Establishment of monitoring schedule and emergency contact framework

Manufacturing initiation:

- If autologous DC vaccine planned: tumor tissue or PBMC collection and shipment to manufacturing facility
- If mRNA neoantigen vaccine planned: tumor + germline DNA sequencing initiation, neoantigen prediction, manufacturing — 6–10 week lead time

Phase 0 ends when (a) all baseline assessments are complete, (b) consent is documented, (c) Phase 1 components are procured and ready to administer, and (d) the patient is medically and logistically prepared.

6.3 Phase 1 — Immune priming

Objective: Establish active anti-tumor immunity before cytoreductive chemotherapy is introduced. Priming must be active when the immunogenic chemotherapy "trigger" is pulled.

Standard components:

- **Intratumoral TLR agonist** (poly-ICLC) into accessible tumor lesions. Twice in week 1 (days 1 and 5), then weekly through end of Phase 1. Each injection at 1

mg or per published protocol; volume adjusted for lesion size.
- **Checkpoint inhibitor** (pembrolizumab 200 mg every 3 weeks, or nivolumab 240 mg every 2 weeks, or equivalent) initiated on day 1.
- **Vaccine first dose** as soon as it is manufactured (typically arrives during weeks 4–10 of overall protocol; can be brought in during Phase 1 or Phase 2 depending on manufacturing timeline).
- **Hyperthermia** (where available): one session weekly during this phase, fever-range (39–40.5°C), 2–4 hours.

Note on poly-ICLC injection frequency: The indication-specific schedules below (Sections 7.3, 8.3, 9.3) use a less-intensive priming schedule (typically 2–3 injections in week 1, then weekly) for operational practicality. The canonical published intensive priming schedule (1 mg three times weekly for 2 weeks, per Salazar/Hammerich/Kalinski protocols — see Section 5.1) may be preferred where institutional capacity permits, as it more closely matches the protocols that produced the abscopal-response and in-situ-vaccination signals on which Mode 2 engagement is based. The choice between schedules is a clinical-implementation decision for the treating team.

Monitoring during Phase 1:

- Weekly clinical assessment with vital signs and adverse event review
- Weekly CBC, basic metabolic panel
- Baseline imaging documented; mid-phase imaging if clinically indicated
- Watch for: injection site reactions (expected, generally manageable), transient febrile responses (expected from poly-ICLC and hyperthermia), immune-related adverse events (uncommon in this phase but possible — see Section 11)

Phase 1 ends when active immune priming is established (typically 2–4 weeks). Indicators include: documented injection-site immune response, in some cases detectable peripheral T cell response to vaccine, no Grade 3+ adverse events requiring interruption, patient is clinically stable and prepared for chemotherapy initiation.

6.4 Phase 2 — Immunogenic trigger

Objective: Add immunogenic-dose chemotherapy as a controlled trigger that releases tumor antigens and amplifies the primed immune response, while continuing immune-priming components.

Standard components (indication-specific selection — see Sections 7–9):

- **Immunogenic chemotherapy** at dose selected per the principles in Section 3.4. Initial cycle at standard or slightly reduced dose with close response monitoring; subsequent cycles adjusted based on response (radiographic + ctDNA where available) and tolerability.
- **Continued checkpoint inhibitor** on standard schedule.
- **Continued intratumoral TLR agonist** at reduced frequency (typically bi-weekly or every 3 weeks during chemotherapy phase, depending on tumor accessibility as cytoreduction progresses).
- **Vaccine** ongoing dosing per manufacturing schedule.

- **IL-15 superagonist** initiated to support T cell persistence through the chemotherapy phase. Suggested schedule: every 2 weeks subcutaneous; dose per Section 5.4 hierarchy (starting 6–10 µg/kg every 2 weeks with escalation toward 15 µg/kg every 3 weeks based on tolerance).
- **Hyperthermia** during this phase: continue weekly or biweekly, ideally timed within 24–72 hours of chemotherapy to enhance synergy.

Monitoring during Phase 2:

- Pre-cycle laboratories (CBC, CMP) before each chemotherapy cycle
- Imaging assessment every 6–9 weeks (or per institutional protocol for the chemotherapy regimen)
- ctDNA at baseline and every 4–6 weeks where assay is available — this is the most sensitive indicator of response and the strongest signal for whether the immunogenic trigger is working
- Immune-related adverse event surveillance (see Section 11)
- Cardiac monitoring (LVEF) if anthracyclines or IL-15 high-dose protocols are used

Phase 2 ends when (a) cytoreductive objective is achieved (radiographic response, ctDNA clearance, or — in neoadjuvant settings — surgical resection performed), (b) toxicity dictates termination, or (c) progression on therapy indicates the protocol is not working for this patient.

6.5 Phase 3 — Sustained engagement

Objective: Protect and amplify the now-established immune response through and beyond the chemotherapy phase. Convert what may be a short-lived effector response into long-lived memory immunity.

Standard components:

- **Continued IL-15 superagonist** — this is the central component of Phase 3. Sustained IL-15 signaling is what converts effector T cells into memory T cells, providing the durable immune surveillance that the framework's Mode 6 engagement targets.
- **Continued checkpoint blockade** through this phase to protect ongoing immune activity from exhaustion.
- **Vaccine maintenance dosing** if applicable.
- **Stromal-modifying agent** and/or **suppression-axis inhibitor** added during this phase if not initiated earlier, depending on tumor type and treatment-response trajectory.
- **Hyperthermia** at reduced frequency (monthly or as tolerated).

Monitoring during Phase 3:

- Clinical assessment every 4–6 weeks
- Imaging every 8–12 weeks
- ctDNA every 6–8 weeks
- Immune phenotyping where available (CD8 T cell counts, memory phenotype assessment) — particularly valuable for assessing whether the framework's Mode

6 hypothesis is being achieved in this patient

Phase 3 ends when sustained engagement is established (typically 6–9 months from start of overall protocol) and the patient transitions to surveillance maintenance.

6.6 Phase 4 — Surveillance / maintenance

Objective: Maintain immune readiness and provide early detection of any relapse.

Standard components:

- **Periodic checkpoint inhibitor** every 3–6 weeks, continuing for ≥1 year total from protocol start
- **Periodic vaccine boost** (if applicable) at 3–6 month intervals
- **Periodic IL-15** at reduced frequency (every 4–6 weeks) for the first 6–12 months of Phase 4
- **Continued ctDNA monitoring** every 2–3 months — the most sensitive relapse-detection modality
- **Imaging** every 3–4 months for the first year, transitioning to longer intervals if disease-free

Duration: Minimum 1 year of overall immunotherapy from protocol start. Continuation beyond 1 year depends on patient response, ongoing risk assessment, and patient preference.

7. Indication 1 — BRCA1/2-mutated triple-negative breast cancer

This indication is presented first because it is the most personally and historically grounded for this framework: the 2011 case that motivated the framework was a Stage IIA (pT2 pN0) high-grade BRCA1-positive triple-negative invasive ductal carcinoma with foci of metaplastic transformation, and the long-term outcome of that case is the empirical anchor for the framework's combinatorial-completeness hypothesis (see Section 13.4 for context). It is also the indication where the framework's components are most accessible and the comparator (KEYNOTE-522 standard of care) is well-defined.

7.1 Indication-specific patient selection

Appropriate candidates:

- Histologically confirmed triple-negative invasive breast cancer (ER-negative, PR-negative, HER2-negative)
- Germline or somatic BRCA1/2 pathogenic variant (or HRD-high tumor on validated assay)
- Stage II–III (neoadjuvant intent), or stage IV with measurable disease, or post-recurrence
- Performance status ECOG 0–2

- Reproductive status: post-menopausal, or premenopausal with reliable contraception throughout treatment

Particularly appropriate situations:

- High-risk early-stage disease where the patient seeks a more aggressive immunotherapy approach than standard KEYNOTE-522 alone provides
- Stage IV disease at presentation or recurrence, where standard chemotherapy alone has historically poor outcomes
- Patients with strong family motivation (BRCA1/2 carriers often have informed family history) for an aggressive multi-modal approach
- Post-recurrence after standard adjuvant treatment, where standard salvage options are limited

Cautions:

- Active brain metastases (treat first, stabilize, then consider this protocol)
- Recent major immune-related adverse event on prior checkpoint blockade
- Significant cardiac dysfunction (anthracycline component requires LVEF >50% baseline)

7.2 Component selection for TNBC

Mode	Component	Standard selection
1	Personalized vaccine	Autologous DC vaccine (CHIPSA / European integrative centers) OR mRNA neoantigen vaccine (where accessible)
1, 7	Immunogenic chemotherapy	Carboplatin AUC 5 + paclitaxel 80 mg/m² weekly OR per KEYNOTE-522 schedule. Doxorubicin/cyclophosphamide considered for Phase 2 second half, *conditionally* (see Section 7.4)
2	Intratumoral TLR agonist	Poly-ICLC 1 mg intratumoral, schedule per Section 6.3
2, supports 1	Hyperthermia	Fever-range whole-body, weekly during Phases 1–2
3	Stromal/vascular modifier	Bevacizumab is *not* standard in TNBC and is not included unless indication-specific reasons (e.g., metastatic disease with rapidly progressive features) suggest it. For most TNBC cases, stromal modification is less critical than in PDAC and is achieved indirectly through immune infiltration
4	Checkpoint inhibitor	Pembrolizumab 200 mg every 3 weeks (per KEYNOTE-522 standard)

Mode	Component	Standard selection
5	Treg depletion	Low-dose cyclophosphamide 50 mg orally daily, *or* metronomic dosing during Phase 1 if not contraindicated by overall chemotherapy plan. CD73 inhibitor not standard for this indication
6	IL-15 superagonist	N-803 (Anktiva), initiated Phase 2; dose per Section 5.4 hierarchy (starting 6–10 µg/kg every 2 weeks, escalating toward 15 µg/kg every 3 weeks)

7.3 Detailed treatment schedule — BRCA1/2 TNBC (early stage, neoadjuvant intent)

This schedule assumes a stage II–III patient pursuing neoadjuvant immunotherapy with the framework. Modifications for metastatic disease and post-recurrence settings follow in Section 7.5.

Phase 0 — Preparation (weeks −3 to 0):

- Complete workup including BRCA status, HRD, PD-L1, full staging
- Initiate autologous DC vaccine manufacturing OR submit tumor for mRNA vaccine manufacturing
- Submit poly-ICLC compassionate-use application if not on hand
- Cardiac baseline: ECG, echo with LVEF
- Informed consent documentation
- Establish monitoring schedule

Phase 1 — Immune priming (weeks 1–3):

Day	Component(s)	Notes
1	Pembrolizumab 200 mg IV; intratumoral poly-ICLC 1 mg into primary lesion (image-guided if not palpable)	First dose of priming
1 (same day or next 24h)	Whole-body hyperthermia session #1, 39–40°C, 2–4 hours	Synergy with first immune dose
5	Intratumoral poly-ICLC 1 mg	Second priming injection
8	Hyperthermia session #2; intratumoral poly-ICLC 1 mg	
8–14	DC vaccine dose #1 once manufactured (may arrive at this stage)	Subcutaneous
15	Intratumoral poly-ICLC 1 mg; hyperthermia session #3	
21 (start of week 4)	Phase 2 initiates	

Phase 2 — Immunogenic trigger (weeks 4–15):

The framework's dose hierarchy from Section 3.4 applies: chemotherapy is the immune-trigger, not the cure. Apply in order of preference:

First choice — assay-guided dosing. Where fresh tumor tissue from the diagnostic biopsy was sent for chemosensitivity testing (Weisenthal-type or similar validated assay), apply the assay-determined doses of carboplatin and paclitaxel for this specific patient's tumor. This is the framework's preferred starting point and matches the empirical approach used in the foundational 2011 case (Section 13.4).

Second choice — framework-default reduced starting dose with response-guided escalation. Where assay-guided dosing is not available: - Carboplatin AUC 3–4 every 3 weeks (reduced from KEYNOTE-522's AUC 5) - Paclitaxel 60–70 mg/m² weekly (reduced from KEYNOTE-522's 80 mg/m²)

Reassess at cycle 2 (week 6) with ctDNA, clinical exam, and imaging if available. If strong response (ctDNA falling, clinical improvement), **continue at the reduced dose** for the remaining cycles — the goal has been achieved without compromising immune competence. If response is suboptimal after 2 cycles, escalate carboplatin and paclitaxel toward KEYNOTE-522 standard doses (AUC 5 / 80 mg/m²) for cycles 3–4.

Third choice — KEYNOTE-522 standard doses with active monitoring and willingness to de-escalate. Where the patient's clinical situation requires standard-of-care doses (institutional preference, rapidly progressive disease, patient choice), use the KEYNOTE-522 backbone: carboplatin AUC 5 every 3 weeks + paclitaxel 80 mg/m² weekly (12 weekly paclitaxel doses, 4 carboplatin doses). Apply ctDNA monitoring every 4 weeks and de-escalate (or transition early to surgery) on strong response signal. The framework does not endorse fixed full-course full-dose chemotherapy regardless of response.

Concurrent throughout Phase 2 (regardless of which dose tier is selected): - Pembrolizumab 200 mg every 3 weeks - N-803 (IL-15 superagonist) initiated at week 4 of Phase 2 (so ~week 5 of overall protocol): every 2 weeks subcutaneous, dose per Section 5.4 hierarchy (starting 6–10 µg/kg every 2 weeks with escalation toward 15 µg/kg every 3 weeks based on tolerance) - Intratumoral poly-ICLC every 2 weeks during Phase 2 (as long as primary tumor remains accessible — typically through weeks 4–9; intratumoral injection becomes impractical once tumor is no longer palpable) - Hyperthermia weekly during weeks 4–9; reduced to biweekly thereafter - DC vaccine boost doses per manufacturing-determined schedule (typically dose 2 at week 5, dose 3 at week 9, dose 4 at week 13) - Low-dose cyclophosphamide 50 mg daily orally (if compatible with carboplatin/paclitaxel marrow tolerance — monitor closely)

Phase 2b — Conditional anthracycline phase (weeks 16–23) — KEY DECISION POINT:

This is where the framework's chemotherapy-as-trigger principle is operationalized most sharply. The conventional KEYNOTE-522 protocol moves to doxorubicin/cyclophosphamide (AC) at this point — a maximally myelosuppressive regimen that risks destroying primed T cells exactly when sustained immunity is most valuable. The framework's logic shifts the default: AC is not the assumed next step but a

conditional addition only where the immune-led response has been insufficient.

Framework default — Option A — proceed to surgery without AC for responders. If by week 15 the patient shows any of: - Excellent radiographic response (≥80% reduction on MRI) - ctDNA clearance or near-clearance - Strong clinical response

then proceed *directly to surgery* without the AC phase. The framework's reasoning is direct: further heavy chemotherapy would risk destroying immunity that has already produced near-complete response, and the persisting immune response (supported through Phase 3 by N-803 and continued checkpoint blockade) provides ongoing surveillance against residual micrometastatic disease. This is a deliberate departure from KEYNOTE-522 standard practice that follows from Path A of the framework principle.

Option B — Modified AC with full immune-protective infrastructure. Where response at week 15 is partial but ongoing, AC may be added with reduced intensity (dose-density modified, growth-factor supported) and with the immune-protective components running throughout: N-803 to sustain T cell pool, continued pembrolizumab, vaccine boost timed to follow each AC cycle for response amplification. Close cardiac monitoring required (LVEF). The principle remains: AC is the trigger refinement, not the primary cure.

Option C — Surgery now, adjuvant AC only if pathology indicates residual disease. Intermediate option where the response is uncertain at week 15 — proceed to surgery, then reserve AC for adjuvant phase only if surgical pathology shows significant residual disease that the immune-led response did not clear.

Selection among A, B, C is a multidisciplinary decision involving the treating oncologist, surgeon, and patient — but the framework's prior is **Option A as the default** for any patient meeting the strong-responder criteria. The framework's central bet is that combinatorial-complete immunotherapy plus moderate-dose immunogenic chemotherapy can replace, not just supplement, maximum-dose myelosuppressive chemotherapy in the responding-patient subgroup. Implementing teams should be prepared to make this de-escalation when the response indicators justify it.

Surgical phase:

Surgery scheduled 4–6 weeks after the final cytotoxic chemotherapy cycle to allow: - Marrow recovery - Wound healing capability (especially relevant if bevacizumab or other anti-angiogenic was used — though typically not in TNBC) - Continued immune activity into the surgical period (a primed immune response may reduce risk of micrometastatic seeding)

Phase 3 — Sustained engagement (post-surgery, weeks 24–52):

- Pembrolizumab 200 mg every 3 weeks until completion of 1-year total immunotherapy course
- N-803 every 2–3 weeks
- DC vaccine maintenance dose every 8–12 weeks
- Hyperthermia monthly through this phase if continuing
- Low-dose cyclophosphamide as tolerated

Phase 4 — Surveillance (year 2 onward):

- ctDNA every 3 months
- Imaging every 4–6 months for first 2 years, then per long-term surveillance
- Maintenance pembrolizumab continued or stopped per institutional decision based on response durability
- Long-term BRCA-related surveillance per guidelines (contralateral breast, ovarian)

7.4 Sequencing principle — restated for clinical clarity

The most consequential decision in this protocol is sequencing — specifically, whether to add immunotherapy onto a fixed chemotherapy backbone (the conventional approach) or to use chemotherapy as a controlled trigger within an immunotherapy-led protocol (the framework's approach).

The framework's approach, as instantiated above, has three operational implications a treating team must accept:

1. **Immunity is established first.** Weeks 1–3 of Phase 1 are pure immune priming with no cytoreductive chemotherapy. This is a departure from conventional neoadjuvant practice. The team must accept that pure immune priming is the right use of the first three weeks.
2. **The conventional "more chemo is more cure" instinct must be examined.** The framework's prediction is that less chemotherapy combined with full multi-mode immunotherapy will outperform more chemotherapy combined with partial immunotherapy. This is not validated by RCT — it is the framework's hypothesis. The Option A (reduced/omitted AC) decision in Phase 2b is where this instinct most directly conflicts with conventional practice.
3. **Response is judged earlier and more sensitively.** ctDNA monitoring, where available, is the central response-assessment tool because it indicates microscopic residual disease far earlier than imaging. The framework's protocols depend on early response assessment to inform de-escalation decisions.

7.5 Modifications for advanced/metastatic TNBC

Metastatic at diagnosis or post-recurrence: The same framework applies with these modifications:

- Phase 0 may be compressed — initial palliative chemotherapy may be needed within days while priming components are being prepared
- Phase 1 immune priming is initiated in parallel with first-line palliative chemotherapy rather than before it, with subsequent intensification once components arrive
- Surgery is not standard; aggressive cytoreduction of oligometastatic disease (SBRT, local ablation) may be considered as part of Phase 2 to release antigens
- Phase 3 sustained engagement becomes the long-term treatment, often continuing indefinitely

- Patient counseling about goals of care — durable disease control rather than cure — is essential

Post-recurrence after standard adjuvant: Where a patient has completed standard adjuvant (typically including doxorubicin/cyclophosphamide), the framework can still be applied with these considerations:

- Marrow reserve assessment before reintroducing chemotherapy
- Choice of chemotherapy in Phase 2 informed by what was used adjuvantly (often gemcitabine or eribulin in this context rather than re-introducing platinum)
- Priming components are more critical, as prior chemotherapy will have depleted naive T cells and recovered immunity needs to be deliberately rebuilt

8. Indication 2 — Pancreatic ductal adenocarcinoma

8.1 Indication-specific patient selection

Appropriate candidates:

- Histologically confirmed pancreatic ductal adenocarcinoma
- Resectable, borderline-resectable, or oligometastatic disease (≤3 metastatic sites)
- Performance status ECOG 0–2
- Adequate biliary drainage (if obstruction was present)
- Adequate hepatic and renal function for mFOLFIRINOX or modified regimen

Particularly appropriate situations:

- Resectable disease where surgery is planned and the patient seeks aggressive perioperative immunotherapy beyond standard adjuvant chemotherapy
- Borderline-resectable disease where neoadjuvant cytoreduction is required and the goal is conversion to resectability
- Post-resection setting where standard adjuvant chemotherapy alone has acceptable but suboptimal recurrence-free survival
- Stable oligometastatic disease where aggressive systemic + local control may produce durable remission

Cautions:

- Uncontrolled biliary obstruction (drain first, treat second)
- Significant ascites or peritoneal carcinomatosis (alter goals of care discussion)
- Severe malnutrition or cachexia (nutritional optimization before protocol initiation)

8.2 Component selection for PDAC

The component selection for PDAC reflects the framework's analysis that PDAC's dominant failure modes are Mode 3 (stromal exclusion — the desmoplastic barrier) and Mode 5 (active suppression — adenosine axis, Treg, MDSC). The protocol therefore emphasizes these.

Mode	Component	Standard selection
1	Personalized vaccine	mRNA neoantigen vaccine (autogene cevumeran-equivalent) where accessible — this is the indication where mRNA vaccine has the strongest published signal. Where unavailable, autologous DC vaccine
1, 7	Immunogenic chemotherapy	mFOLFIRINOX (oxaliplatin highly immunogenic) at moderate dose; gemcitabine + nab-paclitaxel as alternative
2	Intratumoral TLR agonist	Poly-ICLC. *Note: intratumoral injection into pancreatic primary is technically challenging and not routinely performed; this component is most useful for accessible metastatic sites (liver, nodal) where present*
2, supports 1	Hyperthermia	Whole-body fever-range, weekly during active phases. Pancreatic region heating may be added with appropriate equipment
3	**Stromal/vascular modifier — CRITICAL FOR PDAC**	Multiple options, often combined: (a) bevacizumab 5 mg/kg every 2 weeks (vascular normalization); (b) losartan 50 mg daily (stromal/stellate-cell effect); (c) FAK inhibitor if accessible
4	Checkpoint inhibitor	Atezolizumab 1200 mg every 3 weeks (matches autogene cevumeran-protocol use) or pembrolizumab
5	**Suppression-axis inhibitor — CRITICAL FOR PDAC**	Oleclumab (CD73 inhibitor) where accessible. Where unavailable, low-dose cyclophosphamide 50 mg daily continuous through Phase 2–3 plus consider losartan (also has Treg/MDSC effects)
6	IL-15 superagonist	N-803, initiated in Phase 1, every 2 weeks subcutaneous

8.3 Detailed treatment schedule — PDAC (resectable or borderline-resectable)

Phase 0 — Preparation (weeks −4 to 0):

- Complete staging including endoscopic ultrasound for resectability assessment
- Multidisciplinary tumor board review
- mRNA neoantigen vaccine manufacturing initiation (if accessible) — 6–10 week lead time means this must start very early
- Biliary stent placement if obstruction
- Nutritional optimization (often the limiting factor in PDAC patients)
- Poly-ICLC, oleclumab, N-803 procurement
- Informed consent

Phase 1 — Immune priming (weeks 1–3):

Day	Component(s)	Notes
1	Atezolizumab 1200 mg IV; intratumoral poly-ICLC into accessible metastasis (if present and accessible)	First priming; pancreatic primary typically not directly injected
1	Whole-body hyperthermia session #1	
1	Initiate low-dose cyclophosphamide 50 mg daily orally (Mode 5 partial engagement)	Continue throughout protocol unless cytopenia develops
1	Initiate losartan 50 mg daily (Mode 3 stromal effect)	Continue throughout protocol
8	Hyperthermia session #2; intratumoral poly-ICLC (if accessible site)	
14	Hyperthermia session #3	
14	DC vaccine dose #1 if mRNA vaccine not yet available	
22 (week 4)	Phase 2 begins	

Phase 2 — Immunogenic trigger + intensified stromal/suppression engagement (weeks 4–19):

Weeks 4–19: Immunogenic chemotherapy phase. mFOLFIRINOX every 2 weeks for 6–8 cycles total, dose-selected per the framework hierarchy (Section 3.4):

First choice — assay-guided dosing. Where fresh PDAC tissue from diagnostic biopsy or EUS-FNA was sent for chemosensitivity testing, apply the assay-determined doses for oxaliplatin, irinotecan, and 5-FU components.

Second choice — framework-default reduced starting regimen with response-guided escalation. Where assay-guided dosing is not available, the framework's recommended starting regimen (drawn from published reduced-dose mFOLFIRINOX protocols, e.g., NCT04084496): - Oxaliplatin 65 mg/m² IV over 3 hours - Irinotecan 135 mg/m² IV over 90 minutes - Leucovorin 400 mg/m² (or l-leucovorin 200 mg/m²) - 5-FU 2400 mg/m² continuous IV infusion over 46 hours - **No 5-FU bolus** - G-CSF support per institutional protocol

Reassess at cycle 3 (week 8) with ctDNA, CA 19-9, and cross-sectional imaging. If responding (ctDNA falling, CA 19-9 falling, imaging stable or shrinking), **continue at the reduced dose** through cycles 4–8. If response is suboptimal, escalate toward standard mFOLFIRINOX doses for cycles 4–8.

Third choice — standard adjuvant mFOLFIRINOX (Conroy et al., PRODIGE-24, *NEJM* 2018): - Oxaliplatin 85 mg/m² IV over 2 hours - Leucovorin 400 mg/m² IV over 2 hours - Irinotecan 150–180 mg/m² IV over 90 minutes - 5-FU 2400 mg/m² continuous IV infusion over 46 hours - No 5-FU bolus - G-CSF support per institutional protocol

Used where rapid cytoreduction is the priority (e.g., borderline-resectable with progression at diagnosis, large symptomatic primary, time-pressured surgical planning).

Apply ctDNA and CA 19-9 monitoring every 4 weeks and be prepared to de-escalate on strong response. The framework does not endorse fixed full-course full-dose chemotherapy regardless of response.

The framework's prior for resectable or borderline-resectable PDAC patients with adequate time for an immune-led approach is the **reduced starting regimen** — this is the framework's primary recommendation, consistent with the principle that chemotherapy is the immune trigger, not the cure.

Concurrent throughout Phase 2: - Atezolizumab 1200 mg every 3 weeks - **mRNA neoantigen vaccine** weekly × 8 (priming series) once delivered, then biweekly (per autogene cevumeran schedule) - **Bevacizumab 5 mg/kg every 2 weeks** added at week 6 of Phase 2 (after first few cycles of chemotherapy establish baseline tolerance) — Mode 3 vascular normalization - **N-803 every 2 weeks** — Mode 6 throughout - **Oleclumab (if accessible)** at week 8 every 2 weeks — Mode 5 - Continued **low-dose cyclophosphamide** and **losartan** - **Intratumoral poly-ICLC** into accessible metastatic sites every 3 weeks - **Hyperthermia** weekly through week 12, then biweekly

Surgery phase (weeks 20–22):

If resectable conversion or persistent resectability: - Final pre-surgical imaging at week 18 - Final ctDNA at week 18 (key indicator) - Multidisciplinary review for surgical timing - Bevacizumab must be stopped at least 6 weeks before surgery (wound healing) - Immune-priming components (poly-ICLC, vaccine) can continue close to surgery - Whipple procedure or distal pancreatectomy per disease location

If not resectable or progressive metastatic disease, transition to Phase 3 sustained protocol without surgery.

Phase 3 — Sustained engagement (weeks 23–52):

- Atezolizumab every 3 weeks
- mRNA vaccine maintenance per autogene cevumeran schedule (boost doses)
- N-803 every 3 weeks
- Continued cyclophosphamide 50 mg daily, losartan
- Resumed bevacizumab at week 28 if no wound-healing issues (only relevant if not yet resected, OR post-surgical residual disease)
- Oleclumab maintenance if applicable

Phase 4 — Surveillance (year 2+):

- ctDNA every 2 months for year 2 (highest risk recurrence window)
- CT every 3 months for year 2
- CA 19-9 monitoring monthly
- Continued atezolizumab + N-803 + vaccine boosters every 8–12 weeks through year 2
- After year 2, transition to less frequent surveillance per response

8.4 PDAC-specific notes

Manufacturing timing is critical. The mRNA neoantigen vaccine for PDAC must begin manufacturing at the time of diagnostic biopsy. The 6–10 week lead time means the first vaccine doses arrive during Phase 2; this is why the autogene cevumeran trial sequenced immune priming and vaccine *before* chemotherapy completion. Where mRNA vaccine is unavailable, autologous DC vaccine can be initiated more rapidly (typically 2–3 weeks).

Stromal modification has earlier and stronger justification than in TNBC. The desmoplastic stroma of PDAC is the framework's clearest single-mode bottleneck. Bevacizumab + losartan + (where available) FAK inhibition collectively address Mode 3 in a way that is biologically critical here, not optional.

Adenosine-mediated suppression is severe. Where CD73 inhibitor is unavailable, the combination of low-dose cyclophosphamide (Treg depletion) and losartan (MDSC effects) provides partial Mode 5 engagement. Some centers may additionally consider low-dose radiation to local lymph nodes for further Treg modulation, though this is an unproven adjunct.

9. Indication 3 — Microsatellite-stable metastatic colorectal cancer

9.1 Indication-specific patient selection

Appropriate candidates:

- Histologically confirmed colorectal adenocarcinoma, MSS/pMMR confirmed (this is critical — MSI-high tumors should use established immunotherapy approaches, not this protocol)
- Metastatic disease, first-line or after progression on standard FOLFOX/FOLFIRI ± bevacizumab
- Liver-dominant or lung-dominant metastatic disease, with at least one accessible metastatic site for intratumoral injection (this is a feasibility constraint specific to this indication)
- Performance status ECOG 0–2

Particularly appropriate situations:

- First-line metastatic MSS CRC where the patient seeks an aggressive immune-engaging regimen alongside standard FOLFOX + bevacizumab
- Post-FOLFOX-progression where the patient is seeking immunotherapy-based options and is not eligible for trials
- Oligometastatic liver disease where intratumoral injection of multiple lesions is feasible and a durable response would convert palliative to potentially curable

Cautions:

- Untreated obstruction (treat first)
- Diffuse peritoneal carcinomatosis (limited benefit; goal-of-care discussion)

- Liver function compromise from extensive metastatic involvement (limits chemotherapy tolerance)
- DPYD-deficient patients (5-FU contraindication)

9.2 Component selection for MSS CRC

The framework's analysis of MSS CRC is that the standard FOLFOX/bevacizumab backbone *already* provides partial Mode 1, 3, 7 engagement. The protocol's task is to add the missing modes — Mode 2, Mode 4, Mode 6 — on top of the established standard.

Mode	Component	Standard selection
1, 7	Immunogenic chemotherapy	FOLFOX (oxaliplatin is highly immunogenic) at standard dose initially, adjusted by response
1, supports 2	Vaccine	Autologous DC vaccine where available. mRNA neoantigen vaccine generally less accessible for CRC. Peptide cocktail vaccines (KRAS-targeted where applicable) are an alternative
2	**Intratumoral TLR agonist — CRITICAL FOR THIS INDICATION**	Poly-ICLC, image-guided injection into accessible liver metastases by interventional radiology. This is the framework's distinctive addition to FOLFOX/bev
2, supports 1	Hyperthermia	Whole-body weekly during active phase
3	Stromal/vascular modifier	Bevacizumab 5 mg/kg every 2 weeks — *already standard with FOLFOX in this indication*. No change needed
4	**Checkpoint inhibitor — CRITICAL FOR THIS INDICATION**	Pembrolizumab 200 mg every 3 weeks. Note: prior MSS CRC trials of checkpoint blockade *as a single addition* to FOLFOX have shown marginal benefit. The framework's claim is that in combination with Mode 2 and Mode 6 engagement, checkpoint blockade becomes meaningful
5	Suppression-axis	Low-dose cyclophosphamide 50 mg daily through Phase 2. CD73 inhibitor where accessible
6	**IL-15 superagonist — CRITICAL FOR THIS INDICATION**	N-803, initiated Phase 1, every 2 weeks subcutaneous

9.3 Detailed treatment schedule — MSS CRC (first-line metastatic)

Phase 0 — Preparation (weeks −2 to 0):

- Complete staging including liver MRI for full mapping of metastases
- Identify accessible intratumoral injection sites (interventional radiology evaluation)
- DPYD testing
- Initiate DC vaccine manufacturing
- Poly-ICLC and N-803 procurement
- Informed consent

Phase 1 — Immune priming (weeks 1–3):

Day	Component(s)	Notes
1	Pembrolizumab 200 mg IV	
1	Image-guided intratumoral poly-ICLC 1 mg into largest accessible liver metastasis (IR-guided)	First in-situ priming
1	Whole-body hyperthermia session #1	
1	Initiate low-dose cyclophosphamide 50 mg daily	
5	Intratumoral poly-ICLC (same or different metastasis)	
8	Hyperthermia session #2; intratumoral poly-ICLC	
14	Hyperthermia session #3; DC vaccine dose #1 if available	
22 (week 4)	Phase 2 begins	

Phase 2 — Immunogenic trigger (weeks 4–27):

The framework's dose hierarchy from Section 3.4 applies. Apply in order of preference:

First choice — assay-guided dosing. Where a liver metastasis was biopsied (often feasible in MSS CRC given the typical disease pattern) and tissue sent for chemosensitivity testing, apply the assay-determined doses for FOLFOX components.

Second choice — framework-default reduced starting regimen with response-guided escalation. Where assay-guided dosing is not available, the framework's recommended starting regimen: - Oxaliplatin 65 mg/m² IV over 2–3 hours (reduced from FOLFOX-6's 85 mg/m²) - Leucovorin 400 mg/m² IV over 2 hours - 5-FU 2400 mg/m² continuous IV infusion over 46 hours - **No 5-FU bolus** (omission reduces hematologic toxicity, preserves marrow for the immune-led response) - Bevacizumab 5 mg/kg every 2 weeks

Every 2 weeks. Reassess at cycle 3 (week 10) with ctDNA, CEA, and cross-sectional imaging. If responding, **continue at the reduced dose**. If suboptimal, escalate oxaliplatin to 85 mg/m² and add the 5-FU bolus (400 mg/m²) for cycles 4 onward.

Third choice — standard FOLFOX-6 (where rapid cytoreduction is the priority): - Oxaliplatin 85 mg/m² - Leucovorin 400 mg/m² - 5-FU bolus 400 mg/m² + 5-FU 2400 mg/m² continuous infusion over 46 hours - Bevacizumab 5 mg/kg every 2 weeks

Used where disease burden or symptoms require maximum-intensity initial cytoreduction. Apply ctDNA monitoring every 4 weeks and be prepared to de-escalate or transition to oxaliplatin holiday (see below) on strong response.

Oxaliplatin holiday after best response. Established practice in metastatic mCRC, *and aligned with the framework's chemotherapy-as-trigger principle.* After best response (typically 6–8 cycles, often earlier with the framework's immune-led approach), drop oxaliplatin from the regimen — continue 5-FU/leucovorin + bevacizumab as maintenance. The clinical rationale (limiting cumulative peripheral neuropathy from oxaliplatin) is well-established. The framework's additional reasoning: once the immune-led response has been established and the cytoreductive trigger has been pulled, continued maximum-intensity chemotherapy is more likely to damage than help the sustained anti-tumor immune response. Oxaliplatin holiday is the framework's default at the response inflection point — not a tolerability fallback.

Concurrent throughout Phase 2 (regardless of dose tier): - Pembrolizumab 200 mg every 3 weeks - N-803 every 2 weeks subcutaneous - Intratumoral poly-ICLC every 2 weeks (rotating among accessible metastatic sites) - DC vaccine boost doses every 4 weeks - Continued low-dose cyclophosphamide - Hyperthermia weekly through week 12, then biweekly

Phase 2b — Response-directed branching (around week 18–24):

Reassess at week 18: - If radiographic response is excellent and ctDNA is clearing: consider local consolidation of any residual oligometastatic disease (SBRT, RFA, surgical metastasectomy) followed by transition to Phase 3 - If response is partial but ongoing: continue Phase 2 to maximum benefit - If progression: consider switch to second-line approach (FOLFIRI-based backbone with the same immunotherapy framework)

Phase 3 — Sustained engagement (post-best response, weeks 28–52+):

- Continued pembrolizumab every 3 weeks
- N-803 every 3 weeks
- DC vaccine maintenance every 8 weeks
- Maintenance 5-FU/leucovorin or capecitabine ± bevacizumab (per standard maintenance for MSS CRC)
- Continued cyclophosphamide

Phase 4 — Long-term surveillance:

- ctDNA every 2–3 months
- Imaging every 3 months
- Maintenance immunotherapy continued indefinitely or per response

9.4 MSS CRC-specific notes

Intratumoral injection is the framework's distinctive addition. This indication absolutely requires accessible metastases. For patients with diffuse small-volume metastatic disease without injectable lesions, the framework's core Mode 2 engage-

ment is limited and the predicted benefit reduces. Patient selection for this indication should explicitly include this feasibility criterion.

The check on the framework's hypothesis is the appearance of a durable-responder subpopulation. In MSS CRC, conventional treatment produces essentially zero long-term responders — patients respond, progress, and eventually die. The framework predicts that combinatorial-complete coverage will produce a subset of patients (perhaps 15–25%) with truly durable responses lasting years. This is the qualitative signal the protocol is aiming for. Institutions tracking outcomes should specifically watch for this — a small fraction of dramatically durable responses, rather than a uniform shift in median PFS.

Hyperthermia synergy with oxaliplatin is well-documented. Where hyperthermia is available, timing it within 24 hours of FOLFOX infusion is suggested for enhanced effect.

10. Chemotherapy-free pathway — framework-aligned alternative for selected patients

This section describes a parallel implementation path for the framework in which cytotoxic chemotherapy is replaced by alternative immune-trigger modalities — principally stereotactic body radiation therapy (SBRT), oncolytic viruses where licensed, intensified intratumoral immunotherapy, and (in BRCA-mutated TNBC) PARP inhibition. The chemo-free pathway is supported by accumulating but pre-RCT evidence and is appropriate for specific clinical situations where chemotherapy is contraindicated, declined, or impractical. It is not a replacement for the chemo-based protocols in Sections 7–9; it is a parallel option for selected patients.

10.1 Purpose and rationale

The framework's central claim is that combinatorial-complete engagement of all seven failure modes produces qualitatively better outcomes than partial engagement. Chemotherapy serves three functions in the chemo-based protocols: bulk cytoreduction, immunogenic cell death (Modes 1 and 7), and partial Mode 5 effect at metronomic doses. The framework's logic permits these functions to be served by alternative modalities. The historical Coley protocol — which informed the framework's structural argument — produced its clinical signal entirely without chemotherapy.

The chemo-free pathway implements this principle for situations where the chemo-based protocols cannot be used. Such situations include: patients with comorbidities precluding chemotherapy (severe cardiac dysfunction, renal failure on dialysis, severe cytopenia, prior heavy chemotherapy exposure with marrow exhaustion); patients who decline chemotherapy after informed discussion; patients who have already failed multiple lines of chemotherapy and whose tumor biology suggests an immune-led approach may still work; and patients with disease patterns particularly suited to local radiation/ablation approaches (oligometastatic disease, accessible primary tumors).

The pathway also addresses an honest clinical reality: some patients facing the cancers this framework addresses will refuse chemotherapy regardless of evidence. The choice for such patients is not between the chemo-based protocol and the chemo-free pathway; it is between the chemo-free pathway and no immunotherapy intervention at all. Implementing institutions that adopt only the chemo-based protocols leave these patients without a framework-aligned option.

10.2 Evidence base — honest synthesis

The evidence base for chemo-free immune-led combinations varies substantially by indication and by component combination. Implementing teams should know what the literature shows and what it does not.

Stereotactic body radiation therapy plus checkpoint inhibitor — the principal chemo-substitute combination. Across solid tumors, RT + ICI has consistently shown improvements over ICI alone in safety-controlled studies, with the strength of signal varying by tumor type. A 15-study NSCLC meta-analysis (published 2023 in the published literature; verify against the most recent meta-analysis at time of implementation) found hazard ratio for overall survival of 0.72 (95% CI 0.63–0.82) and for progression-free survival of 0.79 (0.70–0.89) for RT + ICI versus ICI alone, with abscopal response rate odds ratio 1.94 (1.19–3.17). In melanoma, the abscopal effect with RT + ICI is well documented across case series and small trials, though combination randomized trials have not produced uniform benefit. In advanced pancreatic cancer, a 2026 systematic review (Clinical and Experimental Medicine 2026;26:45, DOI 10.1007/s10238-025-01848-z) reported 1-year overall survival of 80% for durvalumab + SBRT versus 44% for SBRT alone — a striking signal. **Critical caveats that limit how this should be interpreted:** the same review reported 1-year progression-free survival of only 43% for durvalumab + SBRT (versus 46% for SBRT alone — no PFS benefit), suggesting that the OS signal may partly reflect survivorship and selection effects in small included studies; Grade 3/4 treatment-related adverse events were 33.3% for durvalumab + SBRT (higher than SBRT alone at 21.5%); and pooled data across other ICI combinations was heterogeneous (nivolumab + ipilimumab + SBRT showed only 8% 1-year OS, durvalumab + tremelimumab + SBRT 2%). The durvalumab + SBRT signal is interesting and worth pursuing in compassionate-use contexts, but it should not be presented to patients as a validated effect size — the underlying data are early and the OS-PFS disconnect deserves transparency. In MSS metastatic colorectal cancer, multiple studies (Bassetti Phase 1b NCT02837263; Luke multisite SBRT + pembrolizumab JCO 2018) confirm the combination is feasible and safe but show local control without meaningful systemic benefit beyond checkpoint monotherapy — the weakest evidence base of the four indications.

Triple-negative breast cancer specifically. Single-cell and spatial profiling of patients receiving pembrolizumab plus SBRT (24 Gy in 3 fractions of 8 Gy) before neoadjuvant chemotherapy (Shiao et al., *Cancer Cell* 2024;42(1), NCT03366844, n=50) demonstrated effector T cell expansion and epithelial tumor cell elimination *prior to chemotherapy* in a subset of patients. Critically, the analysis identified **three distinct response trajectories**: R1 responders (n≈9, pre-existing inflamed phenotype) responded to pembrolizumab alone with no clear additional benefit from radiotherapy; other responders required the RT addition. This supports that the immune re-

sponse can be generated by RT plus checkpoint without chemotherapy's contribution, but only in selected patients — patient stratification by baseline immune phenotype matters. Pooled analyses of PEMBRO-RT and MDACC trials further show that ablative SBRT (24 Gy in 3 fractions or 50 Gy in 4 fractions) plus pembrolizumab produces 48–54% ORR versus 20% for pembrolizumab alone in solid tumors. The P-RAD trial (NCT07276880) is currently testing different RT boost doses (9 Gy versus 24 Gy) in TNBC neoadjuvant combination.

Oncolytic virus plus checkpoint inhibitor. The MASTERKEY-265/KEYNOTE-034 Phase III trial (Chesney et al., *JCO* 2023) of talimogene laherparepvec (T-VEC) plus pembrolizumab versus pembrolizumab plus placebo in advanced melanoma was negative for primary progression-free and overall survival endpoints. Real-world case series (Cleveland Clinic, n=10) have reported 90% objective response and 60% complete response rates with T-VEC plus PD-1 inhibitor — substantially higher than monotherapy benchmarks. The honest reading: the Phase III negative result is the more authoritative finding; the real-world signal reflects favorable patient selection.

Intratumoral TLR agonist (Hammerich-style in-situ vaccination). The Hammerich 2019 protocol (Flt3L → low-dose radiation → intratumoral poly-ICLC) in indolent non-Hodgkin's lymphoma produced abscopal responses in a proportion of patients. The framework's solid-tumor extension of this approach is biologically reasonable but lacks completed solid-tumor randomized data.

PARP inhibitors in BRCA-mutated tumors. Olaparib and talazoparib produce DNA damage that can be immunogenic. Combination of PARP inhibitor + checkpoint blockade has been tested in BRCA-mutated breast and ovarian cancers. The MEDIOLA trial (Domchek SM et al., *Lancet Oncology* 2020, DOI:10.1016/S1470-2045(20)30324-7, n=34, NCT02734004) tested olaparib 300 mg twice daily plus durvalumab 1.5 g IV every 4 weeks in gBRCAm HER2-negative metastatic breast cancer (including TNBC), reporting 12-week disease control rate of 80% and 28-week DCR of 50%, with grade ≥3 adverse events in 32%. **Honest nuance:** the trial's authors concluded the combination's activity was *similar to that previously observed in olaparib and durvalumab monotherapy studies* — MEDIOLA did not prove durvalumab adds benefit beyond olaparib alone. The combination is reasonable and well-tolerated; the framework's rationale for including PARP inhibitor + checkpoint in the BRCA-mutated chemo-free pathway is mechanistic (DNA damage + checkpoint blockade) rather than empirical proof of superiority over PARP inhibitor monotherapy. PARP inhibitors remain a reasonable chemo-substitute element specifically in BRCA1/2-mutated tumors.

Overall picture. The evidence base supports a chemo-free pathway in selected indications and selected patients, with the strongest support in TNBC and PDAC and the weakest support in MSS CRC. No completed Phase III RCT validates combinatorial-complete (i.e., all-seven-modes) chemo-free protocols in any of these indications. The pathway is investigational in the most direct sense and should be presented to patients with clear acknowledgment of this status.

10.3 Architecture — the modern Coley method, completed

The chemo-free pathway is the most direct modern expression of the Coley protocol that motivated this framework. William Coley's mixed bacterial vaccine (1891–1936) produced its clinical signal through a coordinated combination that the framework's structural analysis now resolves into specific components. The chemo-free pathway implements those components with modern molecular precision while completing them with the elements Coley's era could not provide.

The framework's central thesis — multi-PAMP innate immune activation. Coley's bacterial vaccine contained diverse pathogen-associated molecular patterns (PAMPs) from *Streptococcus pyogenes* and *Serratia marcescens*, engaging multiple innate immune receptors simultaneously: TLR2 from bacterial peptidoglycans and lipoproteins; TLR4 from lipopolysaccharide-like molecules; TLR9 from bacterial unmethylated CpG DNA; and other innate sensors via additional bacterial-derived molecules. The framework's central observation — *the thesis that motivated the Neo-Coley v2 development (Monteiro 2026)* — is that this **multi-PAMP combination, not any single component, produces the qualitatively distinctive immune activation associated with Coley's documented outcomes.** Single-TLR agonists engage one innate pathway in isolation. Multi-PAMP combinations engage the coordinated broad innate response that the framework's structural argument identifies as essential. Removing chemotherapy from the protocol makes this multi-PAMP engagement *more* central, not less — because the immune-activation burden previously shared with chemotherapy's immunogenic-cell-death contribution now falls entirely on the innate-immune-priming components.

The sustained fever response. Coley's vaccines reliably induced febrile responses lasting hours, often days. The fever itself produced heat-shock protein release (enhancing Mode 1 antigen presentation), endothelial activation (Mode 3 vascular effects), changes in immune cell trafficking, and direct cytotoxic stress on tumor cells whose heat tolerance is lower than normal tissue's. The modern equivalent is **sustained fever-range thermal stress** via whole-body hyperthermia, ideally combined with the fever-inducing pharmacodynamic effects of poly-ICLC and (where available) MBV (Coley fluid) preparations themselves.

Broad antigen release and completion of the framework. Coley's vaccine produced antigen release indirectly through tumor inflammation; the modern equivalent in this chemo-free pathway is SBRT-induced antigen release, or cryoablation/RFA, or oncolytic virus where licensed. The framework is then *completed* with the two elements Coley's era did not provide: Mode 4 engagement via checkpoint blockade (pembrolizumab/nivolumab/atezolizumab/durvalumab), and Mode 6 engagement via IL-15 superagonist (N-803). Together with multi-PAMP innate activation and sustained fever response, this constitutes the combinatorial-complete modern Coley protocol.

Substitutions for chemotherapy's functions:

Chemo's function	Chemo-free substitutes
Bulk cytoreduction	SBRT (local, definitive); oligometastatic local therapy (RFA, microwave, cryoablation, surgical metastasectomy where appropriate); response from multi-mode immune engagement
Immunogenic cell death (Modes 1, 7)	SBRT (highly immunogenic, releases broad antigen repertoire from irradiated lesion); cryoablation (releases antigens in necrotic field); oncolytic virus (T-VEC where licensed; HSV-1 oncolysis generates antigen release and PAMP signaling)
Multi-PAMP innate immune activation (Modes 1, 2 — Coley's core mechanism; the framework's central thesis)	**Combination of intratumoral poly-ICLC (TLR3 agonist) plus, where accessible: MBV (Coley fluid) preparation providing multi-PAMP bacterial activation; topical or intralesional imiquimod (TLR7 agonist) for accessible cutaneous or superficial lesions; CpG ODN (TLR9 agonist) where in trial-accessible; intratumoral BCG for select indications (NMIBC primarily). The framework's prediction is that combinations engaging 2+ TLR pathways simultaneously produce qualitatively different immune activation than poly-ICLC alone.**
Sustained fever response (heat-shock proteins, innate activation, vascular effects)	Whole-body fever-range hyperthermia (39–40.5°C, sustained 2–4 hours) as the primary modality; regional/local hyperthermia where WBH is unavailable; PAMP-induced transient febrile responses (poly-ICLC and MBV both produce dose-dependent fever as their desired pharmacodynamic effect) contribute partial sustained fever response
Mode 5 effect (Treg depletion)	Continued low-dose metronomic cyclophosphamide (50 mg orally daily — technically chemotherapy but at immunomodulatory not cytotoxic doses); CD73 inhibitor where accessible; losartan in PDAC

Hyperthermia availability — practical realism. Whole-body fever-range hyperthermia equipment (infrared-A, water-jacketed, radiative, or other devices) is concentrated at integrative oncology centers (CHIPSA, Klinik St. Georg, Paracelsus Klinik, some U.S. centers, several Japanese and German university hospitals) and is not universally available. Where WBH is unavailable, the framework's modern Coley method is partially but not fully reproducible. Practical substitutes:

- **Regional or local hyperthermia** for the primary tumor site — more widely available than WBH, often via radiation oncology departments that combine hyperthermia with radiotherapy
- **More accessible heat-stress modalities** such as infrared sauna exposure protocols — less precise dose-response, less directly validated against the Coley/Neo-Coley evidence base, but feasible in non-specialized settings; can be done by patients at home with appropriate equipment
- **Intensified multi-PAMP combinations** to partially compensate for reduced fever induction — adding TLR7 agonist (imiquimod) or, where accessible, TLR9 agonist or MBV preparations alongside poly-ICLC, leveraging the PAMP-induced transient febrile responses these agents produce as their natural pharmacodynamic effect

Centers without hyperthermia capacity should explicitly assess whether the framework's multi-mode engagement can still be delivered meaningfully. The framework's prediction is that combinatorial-complete engagement of the other modes can produce significant benefit even with reduced fever induction, but the case-series experience underlying the Neo-Coley v2 framework includes sustained fever-range thermal stress as a core component, and the predicted effect size at centers without hyperthermia capacity may be reduced relative to fully-equipped centers.

Additional chemo-substitute or augmentation components:

- **PARP inhibitor** (olaparib 300 mg twice daily, or talazoparib 1 mg daily) in BRCA1/2-mutated TNBC — produces DNA damage with immunogenic features, partially substituting for platinum chemotherapy's mechanism in this patient population
- **Cryoablation or RFA** of accessible metastatic lesions — produces "in-situ vaccination" via local antigen release in necrotic tumor; can be applied to multiple metastases sequentially; complementary to SBRT
- **Intensified intratumoral poly-ICLC schedule** — the canonical Salazar/Kalinski intensive schedule (1 mg three times weekly for 2 weeks, then biweekly IM boosters) becomes the default rather than the alternative in the chemo-free pathway, given that intratumoral priming carries proportionally more of the Mode 2 engagement burden without chemotherapy's contribution

10.4 TNBC chemo-free pathway

Indication and selection:

- BRCA1/2-mutated TNBC (the indication with strongest mechanistic support for PARP-inhibitor substitution)
- Stage II–III neoadjuvant, or stage IV / metastatic, or post-recurrence
- Patient cannot tolerate or declines chemotherapy
- Performance status ECOG 0–2
- Primary tumor amenable to SBRT (most TNBC cases)

Phase 0 — Preparation (weeks −3 to 0): As Section 6.2. Add: radiation oncology consultation and SBRT planning; biospecimen for PARP-inhibitor eligibility verification.

Phase 1 — Immune priming (weeks 1–3):

The TNBC chemo-free pathway implements the Neo-Coley v2 multi-PAMP + sustained-fever-stress architecture in its most accessible form: primary tumor is typically palpable/superficial (ideal for intratumoral injection and any multi-PAMP combination); WBH equipment is well-tolerated in most TNBC patients; fever-induction synergy with the planned SBRT is well-supported by published data.

Day	Component(s)	Notes
1	Pembrolizumab 200 mg IV; intratumoral poly-ICLC 1 mg into primary breast lesion	Begin intensive priming schedule
1	**Sustained fever-range thermal stress: whole-body hyperthermia session #1, 39–40°C, 2–4 hours.** Where WBH is unavailable: regional/local hyperthermia to breast region, or extended infrared exposure as best available substitute	Per Neo-Coley v2 protocol — central component, not adjunct
1	Initiate olaparib 300 mg twice daily orally (BRCA-mutated patients)	Continued through Phase 2
1	Initiate low-dose cyclophosphamide 50 mg orally daily (Treg depletion)	
1	**Where center has access to MBV (Coley fluid) preparation:** consider MBV addition as multi-PAMP augmentation. Initial subcutaneous or intratumoral dose per institutional protocol; expect transient febrile response as desired pharmacodynamic effect	Multi-PAMP combination is the framework's central thesis (Neo-Coley v2)
1	**Optional multi-PAMP augmentation:** intralesional or topical imiquimod (TLR7 agonist) to accessible cutaneous lesions or post-injection sites; CpG ODN where trial-accessible	Adds TLR pathway diversity beyond poly-ICLC's TLR3 alone
3	Intratumoral poly-ICLC 1 mg	Day 3 of intensive priming schedule
5	Intratumoral poly-ICLC 1 mg	Day 5
5	**Hyperthermia session #2**	Twice-weekly fever-range stress during Phase 1 per Neo-Coley v2
8	Intratumoral poly-ICLC 1 mg; DC vaccine dose #1 if available; MBV dose #2 if applicable	
10	Intratumoral poly-ICLC 1 mg; **Hyperthermia session #3**	
12	**Hyperthermia session #4**	
15	Intratumoral poly-ICLC 1 mg; **Hyperthermia session #5**	

Day	Component(s)	Notes
22 (start of week 4)	Phase 2 initiates	

Note on hyperthermia frequency in this pathway: the schedule above provides twice-weekly hyperthermia sessions during Phase 1, reflecting the Neo-Coley v2 emphasis on sustained fever-range thermal stress as a *core* immune-activation component rather than an adjunct. Where center capacity limits delivery to weekly sessions, the protocol can be adapted accordingly with explicit acknowledgment that the framework's predicted effect size may be reduced. Where WBH is unavailable entirely, multi-PAMP intensification (adding MBV, imiquimod, or other TLR agonists alongside poly-ICLC) partially compensates by augmenting PAMP-induced transient febrile responses.

Phase 2 — Immunogenic trigger via SBRT, weeks 4–10:

- **SBRT to primary breast tumor:** 8 Gy × 3 fractions, delivered over week 4 (days 22, 24, 26). Total 24 Gy in 3 fractions, matching the schedule used in the Shiao et al. (*Cancer Cell* 2024;42(1), NCT03366844) single-cell profiling study where this dose produced immune activation prior to chemotherapy
- **Continued pembrolizumab** 200 mg every 3 weeks throughout
- **Continued olaparib** (BRCA-mutated patients) throughout Phase 2
- **N-803 (IL-15 superagonist)** initiated week 5: 6–10 µg/kg subcutaneously every 2 weeks, escalating toward 15 µg/kg every 3 weeks if tolerated
- **Continued intratumoral poly-ICLC** weekly through week 7 (transitioning to IM boosters thereafter as the irradiated primary becomes less accessible)
- **DC vaccine boost doses** per manufacturing schedule
- **Continued low-dose cyclophosphamide**
- **Hyperthermia** weekly through week 7, then biweekly

Phase 2b — Response assessment at week 10:

- MRI of breast and locoregional nodes
- ctDNA, CA 15-3, CEA
- Clinical exam

Decision branching:

- **Complete or near-complete response:** Proceed to surgery (if neoadjuvant intent) or transition to Phase 3 sustained engagement (if metastatic)
- **Partial response with ongoing trajectory:** Continue Phase 2 components for additional 4–6 weeks, reassess
- **Inadequate response:** Reconsider chemo-based protocol (Section 7), discuss with patient

Surgery (neoadjuvant cohort, weeks 14–16):

- Standard surgical principles
- Continuation of olaparib through perioperative period requires risk-benefit assessment (PARP inhibitor effect on wound healing is generally favorable but data

limited)

Phase 3 — Sustained engagement (post-surgery or post-best-response, weeks 17–52):

- Pembrolizumab every 3 weeks
- N-803 every 2–3 weeks
- Olaparib maintenance (per BRCA-mutated TNBC standard adjuvant indication where the patient is post-surgical — this is established practice per the OlympiA trial standard for BRCA-mutated adjuvant disease)
- DC vaccine maintenance
- Continued cyclophosphamide

Phase 4 — Surveillance (year 2+): As Section 6.6.

10.5 PDAC chemo-free pathway

Indication and selection:

- Pancreatic ductal adenocarcinoma, resectable / borderline-resectable / oligometastatic
- Patient cannot tolerate mFOLFIRINOX or gemcitabine-based chemotherapy
- Performance status ECOG 0–2
- Adequate biliary drainage if obstruction is present
- Tumor accessible for SBRT (most pancreatic primaries with appropriate planning, though anatomical proximity to duodenum and bowel requires careful dose constraints)

Phase 0 — Preparation (weeks −4 to 0): As Section 6.2 with PDAC-specific additions: radiation oncology consultation for pancreatic SBRT planning (technically demanding; requires expertise in respiratory motion management and adjacent organ dose constraints); biliary stent placement if obstruction; nutritional optimization (often the limiting factor).

Phase 1 — Immune priming (weeks 1–3):

The PDAC chemo-free pathway implements the Neo-Coley v2 multi-PAMP + sustained-fever-stress architecture with indication-specific adaptations: pancreatic primary is typically not amenable to direct intratumoral injection, so the multi-PAMP component centers on accessible metastatic sites (where present) and systemic vaccine-priming.

Day	Component(s)	Notes
1	Durvalumab 1500 mg IV every 4 weeks (preferred per durvalumab+SBRT PDAC data) or atezolizumab 1200 mg every 3 weeks	First priming

Day	Component(s)	Notes
1	**Sustained fever-range thermal stress: whole-body hyperthermia session #1, 39–40°C, 2–4 hours.** Where WBH unavailable: regional hyperthermia targeting upper abdomen, or extended infrared substitute	Per Neo-Coley v2 protocol — core component
1	Initiate low-dose cyclophosphamide 50 mg daily	
1	Initiate losartan 50 mg daily (Mode 3 stromal effect)	Continued through protocol
1	**Where center has access to MBV (Coley fluid) preparation:** consider MBV addition for multi-PAMP augmentation; particularly useful in PDAC where intratumoral injection of primary is impractical and systemic PAMP delivery is the alternative path	Multi-PAMP combination per Neo-Coley v2
1, 3, 5, 8	Intratumoral poly-ICLC into accessible metastatic sites (where present); intralesional imiquimod to accessible cutaneous sites if applicable	Multi-PAMP combination via accessible sites
5	**Hyperthermia session #2**	Twice-weekly fever-range stress per Neo-Coley v2
8	DC vaccine or mRNA neoantigen vaccine dose #1 (mRNA preferred for PDAC per autogene cevumeran data); intratumoral poly-ICLC if accessible	
10	**Hyperthermia session #3**	
12	**Hyperthermia session #4**	
15	**Hyperthermia session #5**; intratumoral poly-ICLC if accessible	

Note on hyperthermia in PDAC: PDAC patients may have specific tolerance issues with WBH (cachexia common, ascites in some cases, biliary stent considerations). Hyperthermia tolerance should be assessed individually. Where full WBH cannot be delivered safely, regional hyperthermia to the upper abdomen and pancreatic region (more focused, fewer systemic stress effects) is a reasonable substitute. The multi-PAMP combination retains its central role regardless of hyperthermia delivery.

Phase 2 — Immunogenic trigger via pancreatic SBRT, weeks 4–6:

- **SBRT to pancreatic primary:** Typical regimen 33–40 Gy in 5 fractions (5–6 weekly fractions; total dose dependent on tumor size, location, and organ-at-risk constraints) — based on dosing used in the Keane/Tuli durvalumab + SABR PDAC trial (NCT03245541). Alternative: 25 Gy in 5 fractions for smaller tumors

or when adjacent-organ constraints limit higher dose
- **Continued durvalumab/atezolizumab** on schedule
- **Continued mRNA neoantigen vaccine** weekly × 8 (priming series per autogene cevumeran schedule) once delivered, then biweekly maintenance
- **Bevacizumab 5 mg/kg every 2 weeks** initiated week 6 (after SBRT acute period complete; vascular normalization for Mode 3) — note bevacizumab must be held around any planned surgery
- **N-803** every 2 weeks subcutaneous
- **Oleclumab** (where accessible) every 2 weeks for CD73 inhibition (Mode 5)
- **Continued low-dose cyclophosphamide and losartan**
- **Intratumoral poly-ICLC** into accessible metastases every 3 weeks (where present)
- **Hyperthermia** weekly through week 8, then biweekly

Phase 2b — Response assessment at week 12:

- CT abdomen/pelvis with contrast
- ctDNA, CA 19-9
- Multidisciplinary review for surgical timing if appropriate

Decision branching:

- **Resectable conversion or persistent resectability with response:** Proceed to surgery (Whipple or distal pancreatectomy per disease location), then Phase 3
- **Stable or responding unresectable / oligometastatic:** Continue Phase 2 components through week 19, transition to Phase 3
- **Progression:** Reconsider chemo-based protocol or palliative direction

Phase 3 — Sustained engagement (weeks 13–52):

- Durvalumab/atezolizumab continued on schedule
- N-803 every 3 weeks
- mRNA vaccine maintenance per autogene cevumeran schedule
- Bevacizumab resumption post-surgery (if wound healing complete) for residual disease
- Oleclumab maintenance if applicable
- Continued cyclophosphamide and losartan

Phase 4 — Surveillance (year 2+): As Section 6.6, with CA 19-9 monthly.

10.6 MSS CRC chemo-free pathway — weakest evidence base, most caution required

The published data for chemo-free immune-led approaches in MSS CRC is the weakest of the three indications addressed in this protocol. SBRT plus checkpoint blockade has been shown to be feasible and safe in MSS CRC, but multiple studies have not demonstrated meaningful systemic benefit beyond checkpoint monotherapy. The framework's hypothesis — that combinatorial-complete intervention (not just RT plus checkpoint, but RT plus the full seven-mode component set) could shift this — remains untested.

The chemo-free pathway in MSS CRC should be reserved for specific patient situations: patients who have failed multiple lines of FOLFOX/FOLFIRI-based chemotherapy; patients who cannot tolerate further chemotherapy; patients with oligometastatic liver disease accessible for multi-site local therapy (where the framework's premise of combinatorial-complete engagement is most feasible); patients who have declined chemotherapy after informed discussion. It is not a first-line equal alternative to the chemo-based protocol in Section 9 for chemo-tolerant patients.

Indication and selection:

- Metastatic MSS/pMMR CRC
- Liver-dominant oligometastatic disease (≤5 sites) with all sites accessible for SBRT, RFA, or surgical metastasectomy — this is the disease pattern where the framework's logic translates best to chemo-free implementation
- Patient cannot tolerate or has failed FOLFOX/FOLFIRI-based chemotherapy
- Performance status ECOG 0–2
- DPYD-deficient patients (5-FU contraindication) are a reasonable indication for this pathway

Phase 0 — Preparation: As Section 6.2, with multidisciplinary planning for the local therapy approach (SBRT, RFA, surgical metastasectomy sequence and timing for accessible metastases).

Phase 1 — Immune priming (weeks 1–3): Following the Neo-Coley v2 multi-PAMP + sustained-fever-stress architecture, with MSS-CRC-specific implementation:

- Pembrolizumab 200 mg IV, Day 1
- **Intratumoral poly-ICLC** 1 mg via image-guided injection into accessible liver metastases (IR-guided) — Days 1, 3, 5, 8, 10, 15 (intensive priming schedule, rotating among accessible sites)
- **Sustained fever-range thermal stress: whole-body hyperthermia twice weekly during Phase 1 (Days 1, 5, 8, 12, 15), 39–40°C, 2–4 hours.** Where WBH unavailable: regional hyperthermia of the liver region, or extended infrared exposure substitute
- **Where center has access to MBV (Coley fluid) preparation:** consider MBV addition for multi-PAMP augmentation, particularly valuable in this indication given MSS CRC's relatively cold immune phenotype and the framework's prediction that multi-PAMP combinations (not single-TLR engagement) carry the framework's distinctive signal
- **Multi-PAMP augmentation** (optional, where accessible): intralesional or topical imiquimod (TLR7) to any accessible cutaneous metastasis; CpG ODN (TLR9) where trial-accessible
- Initiate low-dose cyclophosphamide 50 mg daily (Treg depletion)
- Bevacizumab 5 mg/kg every 2 weeks (Mode 3 vascular normalization, already standard in mCRC)
- N-803 initiated week 2 (allowing dose-escalation acclimation)
- DC vaccine dose #1 once manufactured

This intensive multi-PAMP + sustained fever-range thermal stress priming is the framework's most concentrated test in the indication where checkpoint blockade alone has historically produced essentially zero benefit. The Neo-Coley v2 thesis

predicts that combinatorial multi-PAMP innate activation combined with sustained fever-range stress can shift this — but the prediction is unvalidated and patients should be informed clearly.

Phase 2 — Multi-modality immunogenic trigger, weeks 4–14:

- **SBRT or ablation of accessible metastases** delivered in staged fashion across weeks 4–10: SBRT (8 Gy × 3 fractions per site, typically) to 2–3 liver metastases; RFA or microwave ablation to additional accessible metastases; the strategy is to produce multiple antigen-release events from different tumor sites to maximize polyclonal immune engagement (Mode 7)
- **Continued pembrolizumab** 200 mg every 3 weeks
- **Bevacizumab 5 mg/kg every 2 weeks** throughout (Mode 3 vascular normalization) — established practice in metastatic CRC, continues from priming phase
- **N-803** every 2 weeks subcutaneous
- **Intensified intratumoral poly-ICLC** into non-ablated accessible metastases between SBRT/RFA sessions
- **DC vaccine boost doses** per schedule
- **Continued low-dose cyclophosphamide** for Mode 5
- **Hyperthermia** weekly during active treatment phase

Phase 2b — Response assessment at week 14:

- CT and/or MRI liver
- ctDNA, CEA
- PET if any FDG-avid sites remain

Decision branching:

- **Complete response or near-complete (all known disease sites controlled):** Transition to Phase 3 sustained engagement
- **New site or residual disease:** Consider additional local therapy to new accessible sites; continue systemic immunotherapy
- **Progression:** Reconsider chemo-based protocol or palliative direction

Phase 3 — Sustained engagement (weeks 15–52+): As Section 9.3 Phase 3, without FOLFOX maintenance — relies entirely on the immunotherapy backbone.

Phase 4 — Surveillance: ctDNA every 2 months for year 2 (high recurrence risk); imaging every 3 months; aggressive willingness to add further local therapy for any new accessible site detected.

10.7 Safety considerations specific to the chemo-free pathway

Radiation, ablation, and the absence of chemotherapy each change the safety profile relative to the chemo-based protocols.

Radiation-related concerns:

- **Pneumonitis:** Higher concern when chest radiotherapy is combined with checkpoint blockade. For TNBC with primary breast SBRT, pneumonitis risk depends on field geometry and dose. Monitor for new dyspnea, cough; chest CT and pulmonology consultation low threshold

- **Pancreatic SBRT toxicity:** Duodenal ulceration, hemorrhage, biliary stricture risk; requires specialized planning. Acute toxicity typically self-limited; late toxicity (months later) more concerning
- **Hepatic toxicity:** Radiation-induced liver disease risk when treating multiple liver metastases; cumulative dose to normal liver must be respected; ICI-related hepatitis adds complexity

PARP inhibitor-related concerns (TNBC pathway):

- **Hematologic toxicity:** Anemia, thrombocytopenia, neutropenia — monitor weekly initially, monthly once stable
- **Therapy-related myelodysplasia / acute leukemia:** Long-term risk; counseling required
- **Fatigue, nausea:** Common; usually manageable

Concerns related to absence of chemotherapy:

- **Cytoreduction may be slower:** Patients with bulky symptomatic disease may require palliative measures during the immune response development. Pain control, biliary drainage, etc., remain core supportive care
- **Less broad antigen release than chemo provides:** The framework predicts that SBRT + intratumoral priming + multi-mode engagement can compensate, but this is the framework's hypothesis. Implementing teams should be honest with patients about this
- **No marrow toxicity is favorable for immune function** — this is the primary benefit and the basis for the pathway

Adverse-event management otherwise follows Section 11 (Safety, adverse event management, and stopping rules). Radiation-related considerations supplement but do not replace those standards.

10.8 When to switch between pathways

The chemo-free and chemo-based pathways are not mutually exclusive within a single patient's course. Reasonable switching points:

- **Chemo-free → chemo-based:** If Phase 2 response assessment shows insufficient response and the patient could tolerate chemotherapy, transition to chemo-based protocol can be initiated. Time invested in the chemo-free phase is not wasted — the immune priming established in Phase 1 enhances the chemo-based protocol's effectiveness when added later.
- **Chemo-based → chemo-free maintenance:** Patients on the chemo-based protocol who achieve a strong response may transition to chemo-free sustained engagement (Phase 3) earlier than planned, dropping further chemotherapy and continuing only the immunotherapy components plus radiation/ablation of any residual sites.
- **Sequential combination:** For some patients, the optimal protocol may be brief chemotherapy (1–2 cycles for immediate cytoreduction) followed by transition to chemo-free pathway for sustained engagement. This is a clinical-judgment choice not specified by the framework but consistent with its logic.

The decision framework remains the same as in the chemo-based protocols: the response indicators (ctDNA, imaging, clinical exam) drive treatment intensity and modality, not protocol commitment.

11. Safety, adverse event management, and stopping rules

The framework's combinations involve multiple immunologically active agents administered together. Toxicity profiles overlap and may be synergistic. Vigilant monitoring and clear stopping rules are essential. This section provides general guidance; component-specific package inserts and institutional protocols remain authoritative.

11.1 Anticipated adverse event profile

Combination-typical:

- Constitutional symptoms (fatigue, malaise, low-grade fever) — common, expected, generally manageable
- Injection-site reactions from intratumoral poly-ICLC — common, expected, may include local pain, erythema, warmth, transient swelling
- Transient febrile responses from poly-ICLC and hyperthermia — expected pharmacodynamic effect; rarely require intervention beyond supportive care
- Mild rash, pruritus — common with checkpoint blockade
- Nausea, diarrhea — common with chemotherapy components
- Cytopenias — expected with chemotherapy, may be enhanced by other components

Immune-related adverse events (irAEs) requiring vigilant monitoring:

- Pneumonitis (1–5% with checkpoint blockade; potentially enhanced in combination)
- Hepatitis (transaminitis; checkpoint-typical)
- Colitis (checkpoint-typical; may overlap with chemotherapy-related diarrhea — distinguish by endoscopy if persistent)
- Endocrinopathies (hypothyroidism, adrenal insufficiency, hypophysitis, diabetes — variably reversible)
- Myocarditis (rare but potentially fatal; checkpoint-related; baseline troponin and on-treatment troponin monitoring recommended)
- Nephritis
- Neurologic (myasthenia gravis, encephalitis, peripheral neuropathy)
- Cytokine release syndrome (potential with IL-15 superagonist + checkpoint combination, especially at higher IL-15 doses)
- Skin toxicities including rare severe reactions (Stevens-Johnson, TEN)

Component-specific concerns:

- **Bevacizumab:** hypertension, proteinuria, thromboembolism, impaired wound healing (relevant for surgical phases), GI perforation (rare, severe)
- **Anthracyclines (if used):** cardiotoxicity, requires LVEF monitoring

- **Hyperthermia:** dehydration, cardiac stress in patients with marginal cardiac reserve; not appropriate in severe cardiac disease
- **Low-dose cyclophosphamide:** cytopenia (low risk at metronomic doses), hemorrhagic cystitis (rare at these doses)

11.2 Monitoring schedule

Baseline (pre-Phase 1): - Complete metabolic profile, CBC, coagulation, LDH - TSH, free T4, cortisol, ACTH - Troponin, NT-proBNP, ECG, echocardiogram with LVEF - Lipase, amylase - HIV, hepatitis B/C - Pregnancy test (women of reproductive potential)

During Phase 1 (weekly during active priming): - CBC with differential - Comprehensive metabolic panel - Clinical assessment with vital signs, symptom review

During Phase 2 (each chemotherapy cycle): - CBC pre-cycle - CMP pre-cycle - TSH every 6 weeks - Troponin if any cardiac symptoms (chest pain, dyspnea) - Lipase if abdominal symptoms - Cortisol if fatigue out of proportion or other adrenal symptoms

During Phase 3 (monthly): - CBC, CMP - TSH every 8 weeks - Cortisol every 3 months

Throughout (event-driven): - Any new symptom requires assessment for irAE before attribution to other cause - New dyspnea → chest imaging, troponin, evaluate for pneumonitis and myocarditis - New diarrhea → evaluate for colitis (endoscopy if >Grade 2 or persistent) - New rash → assess severity; >Grade 2 may require treatment hold - New fatigue → assess for endocrine cause (TSH, cortisol)

11.3 Stopping and modification rules

Pause-only events (treatment hold, restart when resolved):

- Grade 1–2 irAEs: hold most-likely-culprit component; supportive care; restart when ≤Grade 1
- Grade 1–2 cytopenias: hold chemotherapy until recovery; immunotherapy may continue
- Local injection-site reactions: continue protocol; manage symptomatically

Component-discontinuation events:

- Grade 3 irAE attributable to checkpoint blockade: discontinue checkpoint inhibitor; manage with corticosteroids per standard irAE guidelines; continue other components if not contributing
- Grade 3 myocarditis: discontinue checkpoint AND IL-15 immediately; aggressive workup and management
- Grade 4 irAE of any kind: discontinue all immunotherapy components; reassess goals of care

Whole-protocol stopping events:

- Two consecutive Grade 3+ irAEs from any component
- Any Grade 4 irAE

- Progressive disease that has clearly not responded to the protocol (assessed at appropriate response-assessment timepoints)
- Patient request to stop
- Decision in shared discussion that protocol is not benefiting the patient

11.4 Management of selected severe events

Suspected immune-related pneumonitis: 1. Hold checkpoint inhibitor, IL-15, and intratumoral injection 2. Chest CT with contrast 3. Pulmonology consultation 4. If confirmed Grade 2–3: methylprednisolone 1–2 mg/kg/day with slow taper; consider infliximab if steroid-refractory 5. Permanent checkpoint discontinuation if Grade 3+

Suspected immune-related colitis: 1. Hold checkpoint inhibitor 2. Rule out infection (C. difficile, CMV) 3. Endoscopy if >Grade 2 or persistent 4. Corticosteroids (methylprednisolone 1–2 mg/kg/day); infliximab or vedolizumab if steroid-refractory

Suspected myocarditis: 1. Immediate discontinuation of checkpoint inhibitor and IL-15 2. Troponin, BNP, ECG, echocardiogram, cardiac MRI 3. Cardiology consultation; ICU admission threshold low 4. High-dose methylprednisolone (1 g/day × 3 days, then taper) 5. Component never resumed

Cytokine release syndrome (rare, IL-15 + checkpoint combinations): 1. Hold immunotherapy 2. Supportive care; tocilizumab if Grade 2+ 3. Dose reduction or discontinuation of IL-15 going forward

12. Documentation, outcomes tracking, and contribution to learning

12.1 Required institutional documentation

For each patient treated under this protocol, institutional records should include:

- Indication, staging, molecular profile at presentation
- Specific protocol modifications from this framework, with rationale
- All component sources (manufacturers, lot numbers, expanded-access authorizations)
- All dose modifications and the events that prompted them
- Imaging assessments and ctDNA results at each timepoint
- All adverse events with severity, attribution, and management
- Patient-reported outcomes (quality of life, symptom assessment)
- Surgical pathology where applicable (pCR / RVG grading for TNBC; resection margins and lymph node status for PDAC; etc.)
- Survival outcomes and recurrence status at standard timepoints

12.2 Contribution to learning

Compassionate-use protocols, when properly documented, contribute to the field's collective understanding even though individual cases do not constitute RCT evidence. Institutions adopting this framework are strongly encouraged to:

1. **Maintain a structured case registry** of all patients treated, with consent to retain de-identified outcomes data
2. **Periodically review outcomes** internally to identify protocol elements associated with better or worse responses
3. **Publish case series** where outcomes meaningfully inform the field — particularly any cases with durable complete responses (the framework's predicted distinctive signal) or any with unexpected toxicity
4. **Coordinate with the framework's research papers** — institutions treating multiple patients with the framework should make their outcomes data available for systematic review if the framework moves toward RCT validation
5. **Share lessons** through integrative oncology consortia, particularly across centers using similar protocols

12.3 Patient communication and expectations

Patients deserve clear, honest communication throughout. Key themes:

- The protocol is investigational and the framework supporting it has not been validated by RCT
- The framework's predicted benefits are hypotheses, not established results
- The protocol may not work, and the patient may experience significant toxicity for no benefit
- The most likely outcome for any individual patient is uncertain
- Outcomes will be different for different patients; we cannot predict which patients will respond dramatically and which will not
- The patient can withdraw consent and stop the protocol at any time
- Standard supportive and palliative care continues to be available alongside the protocol

13. Limitations and honest acknowledgment

This document presents a clinical protocol framework. It is appropriate to state plainly what this framework is, what it is not, and what its serious limitations are.

13.1 What this framework is

A structural argument that combinatorial-complete engagement of seven failure modes of anti-tumor immunity will produce qualitatively better outcomes than partial-mode engagement, instantiated as concrete protocols for three indications, adapted for clinical use in compassionate-use settings.

The framework is supported by: - Coherent mechanistic biology - The historical Coley case series and its modern integrative-oncology continuation - The autogene cevumeran trial (a multi-mode protocol producing the strongest immunotherapy signal in PDAC, far stronger than anything single-agent immunotherapy has produced in that disease) - The KEYNOTE-522 result (a partial multi-mode protocol producing meaningfully better outcomes than chemotherapy alone in TNBC) - The structural

argument that current single-mode failures in MSS CRC, PDAC, and TNBC are explained by which modes are limiting in each - Individual case experience including the foundational case discussed in Section 13.4

13.2 What this framework is not

It is not RCT-validated. There is no Phase III trial in which a combinatorial-complete protocol of the kind proposed here has been compared against standard of care across a defined population. The proposed BREAKTHROUGH-1, -2, and -3 trials in Paper 4 of the companion series are the trials that would test the framework's central prediction; they have not been conducted.

It is not a description of the standard of care. Standard of care in 2026 for the three indications discussed is conventional chemotherapy plus, in some cases, single-mode immunotherapy. The framework's protocols deliberately depart from standard of care in ways that the framework's logic justifies but evidence does not yet definitively support.

It is not free of risk. The combinations described carry the additive and possibly synergistic toxicity of multiple immunologically active agents. Patients can be harmed by these protocols. The decision to offer them rests on the judgment that the predicted benefit, in patients for whom standard options are insufficient, justifies the risk — but the assessment is irreducibly judgment-based.

It is not a substitute for clinical trial participation when trials are available. Where eligible patients can access relevant clinical trials, trial enrollment is preferable, because it generates the evidence that will eventually bring effective protocols to all patients.

13.3 Why offer this protocol at all

The argument for offering combinatorial-complete protocols in compassionate-use settings, despite the absence of RCT validation, rests on three premises:

The structural case is strong. The framework's mechanistic argument is coherent and the empirical pattern across decades of immunotherapy development matches its predictions: dramatic results where single-mode interventions suffice; translational difficulty where multi-mode failure operates.

The components are well-characterized individually. Every component in the protocols has an established safety profile from individual-agent use. The novelty is in the combination, not in any single component.

The alternative is denial of access during the years required for RCT validation. For patients with the cancers the framework addresses, especially those with metastatic or recurrent disease and limited time, the alternative to compassionate-use combination protocols is standard of care that the framework's analysis predicts will continue to underperform. That alternative is not ethically neutral.

The framework's bet is that combinatorial completeness matters more than the absence of any individual component, and that institutions with the legal authority to

offer combination protocols outside RCTs should consider doing so for appropriately selected patients with full informed consent.

13.4 The foundational case

The framework's existence reflects a single 2011 case that the author cannot honestly omit from this document. A patient with Stage IIA (pT2 pN0) high-grade BRCA1-positive triple-negative invasive ductal carcinoma with foci of metaplastic transformation received a treatment course in two phases:

Phase 1 — Three-week intensive immune-priming at CHIPSA Hospital, Tijuana. Coley toxins (mixed bacterial vaccine sourced via the institution from MBVax Bioscience, Canada) administered under fever titration; autologous tumor antigen vaccine prepared from the patient's biopsy specimen; weekly whole-body fever-range hyperthermia (39–40°C, sustained 2–4 hours per session).

Phase 2 — Home continuation of Coley toxins by the patient's family, on the dosing schedule established at CHIPSA, sustained through the surgical recovery period and continuing during the parallel low-dose chemotherapy phase. The Coley toxin stock for the home phase was obtained from CHIPSA at the conclusion of the intensive phase.

Parallel components throughout both phases: Assay-guided low-dose cisplatin + gemcitabine, selected by ex-vivo chemosensitivity testing (Wiesenthal Cancer Group), administered at reduced dose by a US oncologist willing to depart from standard anthracycline–taxane TNBC adjuvant practice. Bilateral mastectomy with sentinel lymph node biopsy (therapeutic left, prophylactic right reflecting BRCA1+ status) on April 5, 2011 at South Miami Hospital — the surgical pathology confirming Stage IIA classification.

In framework terms, this protocol engaged:

- **Multi-PAMP innate immune activation (Modes 1, 2)** via the mixed bacterial Coley preparation engaging TLR2, TLR4, and TLR9 simultaneously
- **Mode 1 antigen presentation augmentation** via the autologous tumor vaccine, plus heat-shock-protein cross-presentation from sustained fever-range thermal stress
- **Sustained fever-range thermal stress (39–40°C)** — a load-bearing component of the framework, addressed below in §13.5 — via both weekly WBH during Phase 1 and pyrogenic response to Coley toxin titration through Phases 1 and 2
- **Mode 1 / Mode 7 antigen release and broad immunogenicity** via the assay-guided low-dose chemotherapy at controlled immunogenic doses
- **Multi-month duration** of immune-priming components — extending well beyond the 2–4 week regimens characteristic of most modern bacterial immunotherapy trials

The patient is alive in 2026 — fifteen years later, no evidence of recurrence. Published 5-year overall survival for Stage IIA metaplastic TNBC ranges from approximately 50% to 70% across series; the observed outcome is favorable for this subtype. The 2011 protocol was, in the framework's terms, a near-complete multi-mode protocol

that integrated four to five of the seven failure modes simultaneously, with the critical sequencing of immunity-before-cytoreduction and the four-condition Coley thesis preserved (combinatorial PAMP activation + sustained fever-range thermal stress + multi-month duration + immune preservation through dose moderation).

This is one case. It does not prove the framework. The author's purpose in citing it is not to claim that one case can validate a protocol — it cannot — but to acknowledge honestly what motivated the structural analysis that became the framework. The hypothesis that combinatorial completeness produced a qualitative effect in that case is a hypothesis. The framework's research papers propose the trials that would test the hypothesis across populations. This document proposes how the same combinatorial logic can be offered to appropriately selected patients in the interval before those trials are completed.

The case is also the reason this document specifies CHIPSA among the appropriate institutions: not as endorsement of any single center, but in recognition that the kind of multi-mode integrative practice the framework formalizes is exactly the practice that CHIPSA and analogous centers have been conducting for decades. The framework offers a structural account of why what those centers do can sometimes work, when it does, and a more precise, modernized version of the protocol architecture for clinical adoption.

13.5 The fever-range thermal stress requirement — not optional

The framework's central thesis, articulated most directly in the companion Neo-Coley v2 paper, holds that durable Coley-type responses require *four* conditions in combination: combinatorial PAMP activation across multiple innate immune sensors, **sustained fever-range thermal stress at 39–40°C as the dosing endpoint**, multi-month treatment duration, and preservation of host immune function. This document, in operationalizing the framework across indications, must preserve all four. The fever-range thermal stress component is the one most easily lost in implementation, and the one whose loss most directly explains the failure of modern bacterial immunotherapy trials to reproduce Coley's historical response rates. It is therefore worth restating explicitly: **sustained fever-range thermal stress is not an optional adjunct to be added when convenient. It is a load-bearing component of the framework.**

The mechanistic case for this requirement, developed in detail in Section 4 of the Neo-Coley v2 paper and summarized here for the implementing clinician, rests on five independent effects of thermal stress in the 39–40°C range. **First**, heat-shock proteins (HSP70, HSP90) released from tumor cells under thermal stress chaperone tumor antigens into the cross-presentation pathway of dendritic cells, producing CD8+ T-cell activation with substantially higher efficiency than antigen release in the absence of thermal stress — the molecular substrate of the in-situ vaccination effect classically attributed to Coley's therapy. **Second**, endothelial activation produced by fever-range thermal stress increases lymphocyte trafficking into tumor tissue via L-selectin- and ICAM-1-dependent mechanisms (the work of Evans, Repasky, and colleagues at Roswell Park). **Third**, neutrophil recruitment and respiratory burst function are augmented through G-CSF/CXCL8-dependent mechanisms. **Fourth**, natural

killer and γδ T-cell stimulation is enhanced. **Fifth**, direct cytotoxic stress on tumor cells whose heat tolerance is lower than normal tissue's contributes to antigen release and immunogenic cell death. These mechanisms operate cooperatively and depend on the *sustained* nature of the thermal stress — single fever spikes are insufficient.

Achieving fever-range thermal stress in the implementing clinic. Two primary routes:

1. **Whole-body fever-range hyperthermia equipment** (infrared-A, water-jacketed, radiative, or other devices), with patients heated to 39–40°C and sustained at that range for two to four hours per session, ideally weekly during active treatment phases. This is the canonical method and is available at integrative oncology centers including CHIPSA Hospital (Tijuana), Klinik St. Georg (Bad Aibling), Paracelsus Klinik (Lustmühle), and several Japanese and German university hospitals. Regional or local hyperthermia — more widely available, often via radiation oncology departments — is a partial substitute targeting the primary tumor site only.
2. **Fever-titrated PAMP dosing**, in which the Coley toxin or multi-PAMP cocktail dose is escalated until the patient reliably develops sustained 39–40°C fever in response to the pharmacodynamic effect. This route obviates the need for hyperthermia equipment but requires dose titration in early sessions and careful temperature monitoring. The patient's own pyrogenic response — the same mechanism Coley exploited in 1891 — delivers the thermal stress.

Where neither route is achievable, the framework's predictions about durable response may not apply. A protocol that engages multi-PAMP and the other framework modes but fails to achieve sustained fever-range thermal stress is, in the framework's terms, an incomplete implementation. It may still benefit the patient — the other modes engaged are not without value — but it cannot be expected to reproduce the qualitative response the framework predicts for combinatorial-complete protocols.

The empirical anchor reinforces this. The 2011 case described in §13.4 included weekly whole-body hyperthermia at 39–40°C during the three-week intensive phase at CHIPSA, and sustained fever-range pyrogenic response to Coley toxin titration through both phases. The fever component was not optional and was not omitted. Any implementing clinician using this protocol document is asked to take the same position: fever-range thermal stress at 39–40°C is required, sustained through the active treatment phases, by hyperthermia equipment where available, by fever-titrated PAMP dosing where not, by both in combination where possible.

14. References and companion documents

Primary companion papers

- Monteiro EPD. *Combinatorial completeness in cancer immunotherapy: a structural framework for addressing the seven failure modes of immune-mediated tumor control*. 2026. [Paper 3 of the series — Zenodo, full citation upon publication]

- Monteiro EPD. *Combinatorial-complete immunotherapy protocols: three proposed trial designs testing the seven-mode framework in immunotherapy-refractory cancers*. 2026. [Paper 4 of the series — Zenodo, full citation upon publication]
- Monteiro EPD. *Neo-Coley v2: A Unified Framework for Combinatorial PAMP Immunotherapy with Sustained Fever-Range Thermal Stress in Cancer*. 2026. Zenodo. doi:10.5281/zenodo.20322632

Key clinical-evidence citations

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Full reference list is in the companion research papers (Paper 3 and Paper 4).

Appendix A — Component availability quick-reference

Component	Standard source	Compassionate-access pathway	Realistic timeline
Poly-ICLC (Hiltonol)	Oncovir, Inc. (Washington DC)	Direct application to manufacturer + institutional IRB	2–8 weeks
Autogene cevumeran (mRNA neoantigen)	BioNTech/Genentech	Trial enrollment or specific compassionate-use request	Currently very limited outside trials
Autologous DC vaccine	Multiple centers (CHIPSA, Klinik St. Georg, others)	Treatment at the center	2–4 weeks from tumor sample

Component	Standard source	Compassionate-access pathway	Realistic timeline
Pembrolizumab	Merck (commercial)	Standard prescription	Days
Atezolizumab	Genentech (commercial)	Standard prescription	Days
N-803 / Anktiva	ImmunityBio (commercial)	Standard prescription (off-label outside NMIBC)	Days–weeks
Bevacizumab	Genentech (commercial; generics)	Standard prescription	Days
Losartan	Generic	Standard prescription	Days
Oleclumab	AstraZeneca	Trial enrollment or expanded access	Weeks–months
Low-dose cyclophos-phamide	Generic	Standard prescription	Days
Whole-body hyperther-mia	Equipment-dependent	Institutional capability	Established at qualified centers
mFOLFIRINOX / FOLFOX compo-nents	Generic	Standard prescription	Days

Appendix B — Pre-treatment patient checklist

- ☐ Diagnosis histologically confirmed
- ☐ Complete molecular characterization (BRCA, HRD, MSI, PD-L1, TMB as applicable)
- ☐ Full staging completed (imaging, labs)
- ☐ Performance status documented (ECOG)
- ☐ Major organ function adequate (cardiac echo, renal, hepatic, marrow)
- ☐ Autoimmune disease screen
- ☐ Active infection ruled out
- ☐ Pregnancy/contraception addressed
- ☐ Trial eligibility considered and discussed
- ☐ Patient understands and accepts the investigational nature of the protocol
- ☐ Written informed consent completed
- ☐ Institutional ethics/IRB approval obtained where required
- ☐ Compassionate-use applications submitted for required components
- ☐ Vaccine manufacturing initiated (if applicable)
- ☐ Component procurement timeline coordinated with treatment schedule
- ☐ Baseline ctDNA, immune profiling collected where available
- ☐ Patient and family logistics arranged for protocol duration

Appendix C — Sample one-page treatment overview for patient/family

This appendix provides a sample plain-language summary that institutions may adapt for patient and family communication. It is not a substitute for institutional informed-consent documentation.

Your treatment plan

The protocol your medical team is offering combines several treatments together to engage your immune system against the cancer from multiple directions at the same time. Rather than one treatment at a time, this approach uses several treatments in a carefully sequenced way.

The treatments include: - Medicines and injections that “wake up” your immune system and teach it what to look for - Treatments that remove the “brakes” cancer puts on your immune system - Carefully chosen chemotherapy at controlled doses, used to expose cancer cells so the immune system can find them - A medication that helps the immune response last for the long term - Possibly whole-body warming (hyperthermia) to support the response

The order matters: we activate your immune system first, then use the other treatments to support and amplify what your immune system is doing. This is different from the conventional approach of giving chemotherapy first and adding immune treatments later.

What we hope for: That the combination produces a stronger and more lasting response against your cancer than any single treatment could.

What we cannot promise: This is an investigational combination, based on a framework that has not yet been tested in large clinical trials. It may not work. We cannot predict your individual response.

Risks: Like all cancer treatment, this carries side effects. Some are common and manageable; others can be serious. Your team will monitor you closely and adjust treatment as needed.

Your choice: You can decide to stop the treatment at any time. You will continue to receive supportive care regardless.

Questions: Please ask your treating physician about any aspect of this plan you do not understand.

End of document.