IMA EMERGING TRENDS IN MEDICINE

NEW CANCER INSIGHTS ON FRONTLINE TREATMENT

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INDEPENDENT™ MEDICAL ALLIANCE

EMERGING TRENDS IN MEDICINE

New Cancer Insights on Frontline Treatment

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Functional Medicine

Triple Negative Breast Cancer, Case Review

- 52 year old postmenopausal White Female, Hispanic Ethnicity
- Elementary Music Teacher, planning retirement after 30 years
- Pianist/Organist at church
- Overweight, Type 2 Diabetes with associated Stage 3 CKD, mild neuropathy in feet
  - HgbA1c runs around 7.5. Poor glycemic control on oral meds.
  - Elevated Insulin level – Insulin Resistance
  - Metabolic dysfunction-associated steatohepatitis (MASH) with mild increase in LFTs
- HTN and Hyperlipidemia
- No major surgeries
- Married, two adult sons
- Mother died at age 48 from Ovarian Cancer

Triple Negative Breast Cancer, Case Review

- Screening mammograms – she had a couple done in her 40s, negative
- March 2020, at age 50, she had a screening mammogram scheduled and was cancelled during COVID pandemic lockdown and she never rescheduled
- March 2021, she elected to take Pfizer COVID vaccine x2, and got a booster in Sept 2021
- March 2022, she noticed a rapidly enlarging mass deep in her right breast and fullness in her right axilla.
- Mammogram and sonogram revealed a 5.5 cm right UOQ mass + 3 cm axillary LN
- Biopsies of breast mass and axillary LN performed

Triple Negative Breast Cancer, Pathology

- Grade 3, Invasive Carcinoma, basal markers +, ER 0%, PR 0%, Her2 0%, Ki-67 60%
- Triple Negative Breast Cancer (both the breast and axillary LN bx positive)
- Clinical stage IIIC (T3 N1 M0)
- No Oncotype DX indicated
- Staging scans show no metastatic disease
- Hereditary Breast Cancer testing – BRCA2 mutation positive
- Multidisciplinary consult and treatment planning with
  - Breast Surgery
  - Medical Oncology
  - Radiation Oncology

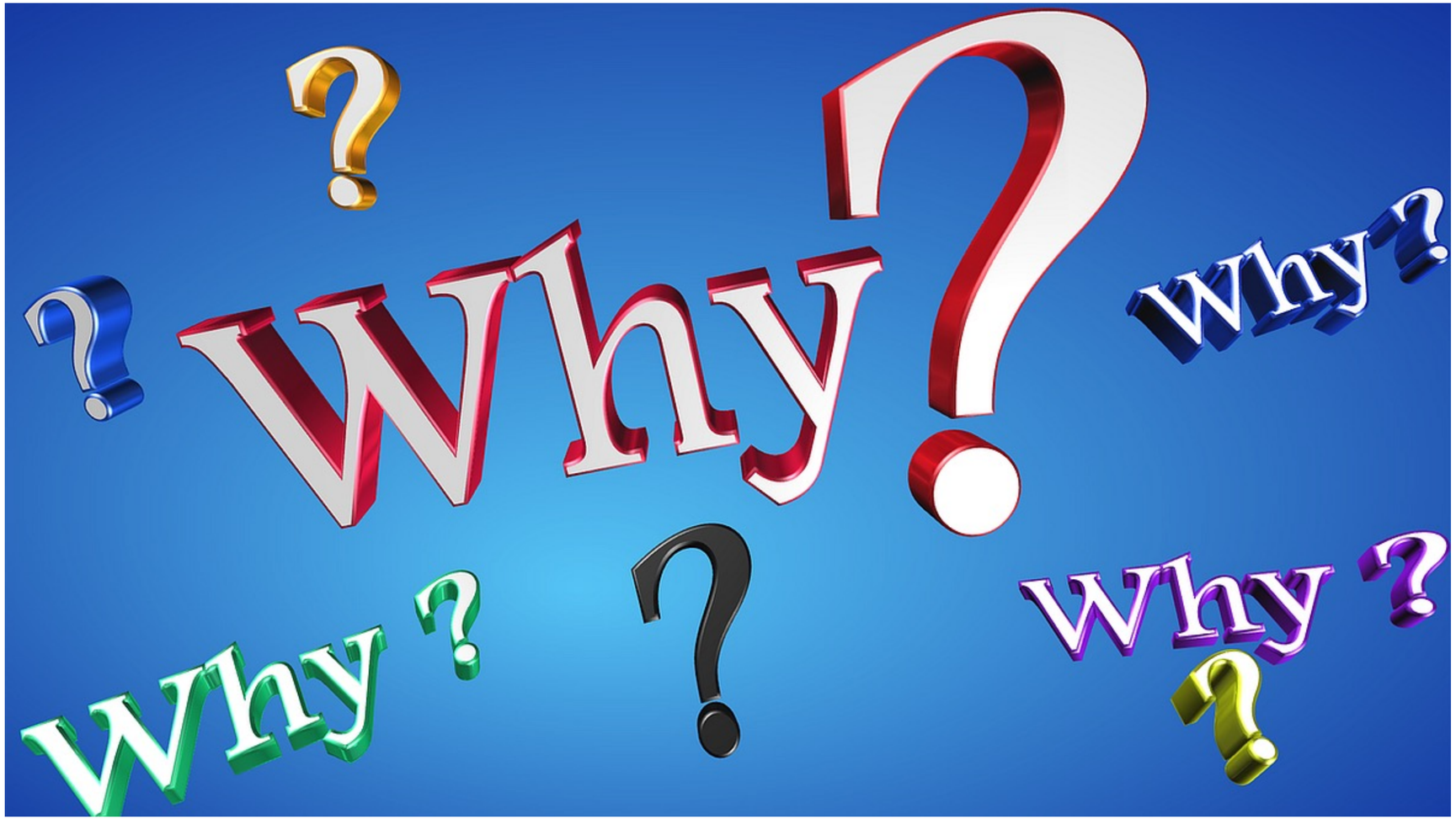
Triple Negative Breast Cancer, Treatment Recommendations

- Neoadjuvant (presurgical) chemoimmunotherapy (Keynote -522 trial)
  - Pembrolizumab D1 + Paclitaxel D1, 8, 15 + Carboplatin AUC=5 q21 Days x12 Weeks, Followed by Pembrolizumab D1 + Doxorubicin + Cyclophosphamide + Peg-Filgrastim support q21 Days x12 weeks
  - (Port placement, Echocardiogram)
- Followed by Surgery
  - Since BRCA2 positive, shared decision-making: Right mastectomy and right sentinel LN axillary dissection + prophylactic left mastectomy
  - Breast reconstruction
- Review of post surgical path to determine residual invasive disease post-neoadjuvant treatment
  - ypTNM status: Stage IIA ypT1c ypN1a grade 3, 1.5 cm residual tumor, 3/12 LN 1 cm, +ENE

Triple Negative Breast Cancer, Treatment Recommendations

- Followed by Adjuvant Pembrolizumab IV q21 Days for up to 27 weeks
  - Consider Phase 3 clinical trial randomized study of Datopotamab Deruxtecan +/- Durvalumab vs Investigator's choice
- Post Mastectomy Radiation Therapy (PMRT) + Regional Nodal Irradiation (RNI)
  - Consideration based on tumor size, +LN status, Staging
  - Timing, Autologous vs. Implant
  - Moderate hypo fractionation 40 Gy in 15 fx
- Adjuvant bisphosphonate therapy with zolendronic acid IV q6m x3 years
- gBRCA1/2- Mutated
  - Adjuvant PARP inhibitor Olaparib 300 mg BID x1 Year
  - Prophylactic TAH/BSO
- No hormonal therapy with Aromatase Inhibitor or Tamoxifen

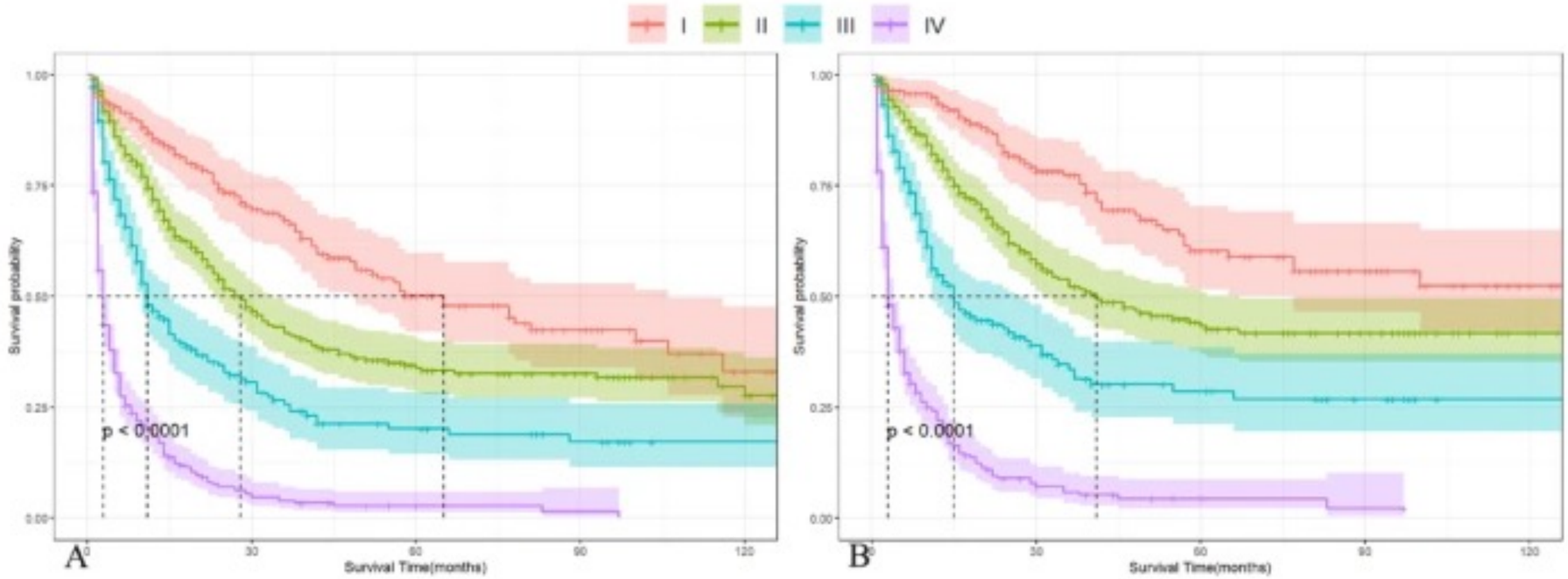
WHY, WHY, WHY, WHY, WHY!?!?!



Triple Negative Breast Cancer, Case Review

- Because Triple Negative Breast Cancer has the capacity for:
  - Early recurrence
  - Relentless progression
  - Kills without discrimination and without mercy

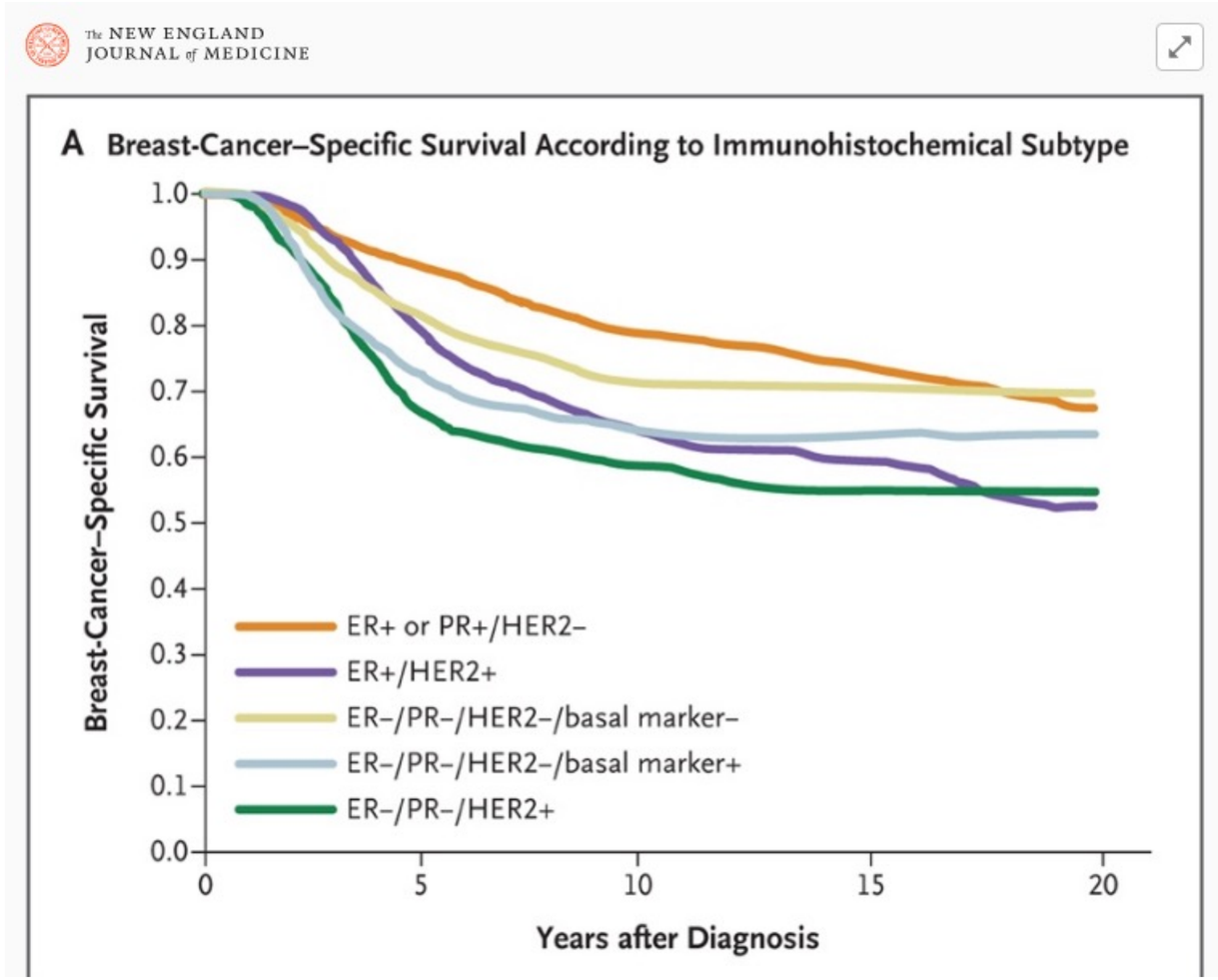
Natural history and prognostic nomogram of untreated triple negative breast cancer based on SEER database



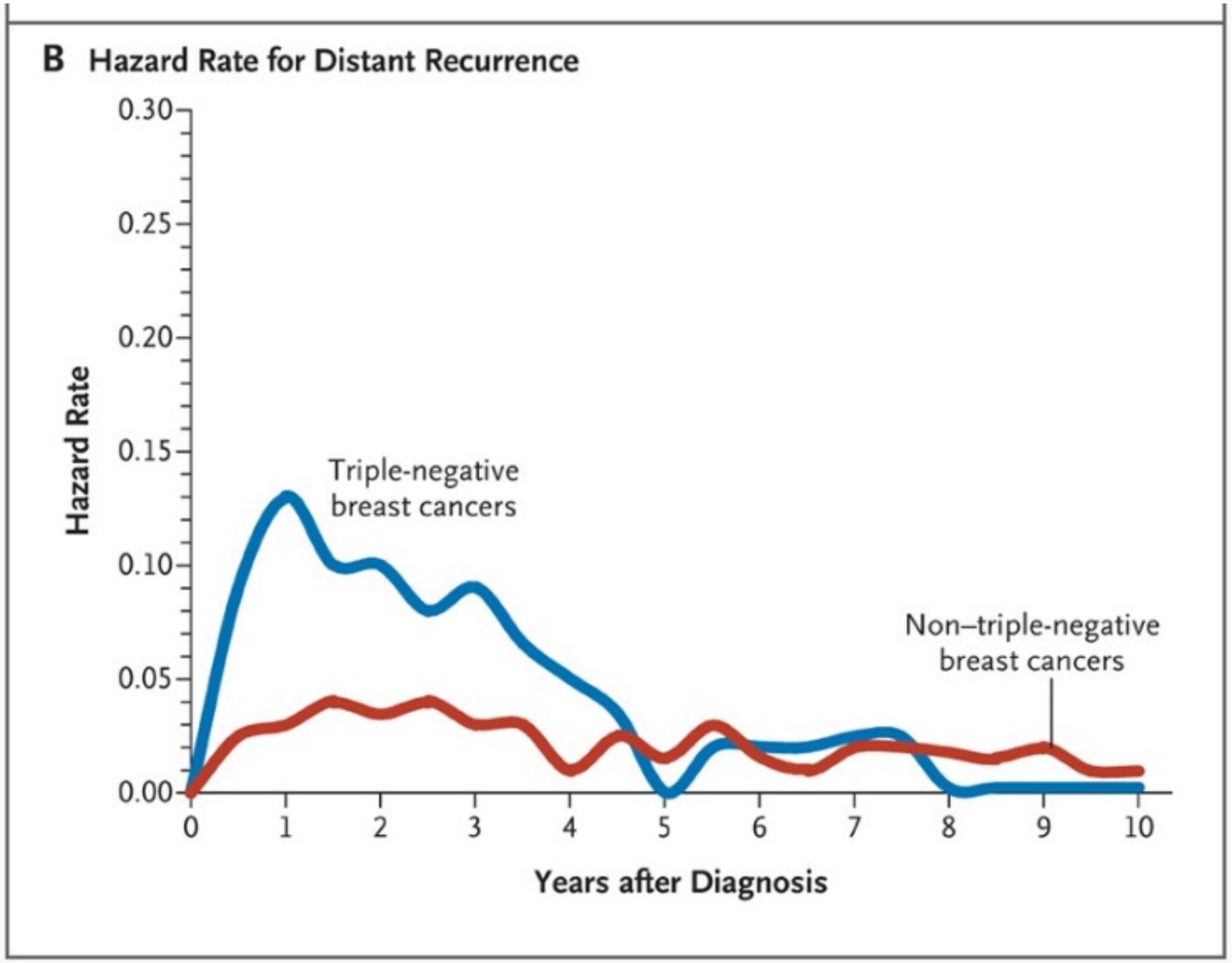
Survival curve for untreated TNBC patients at different stages. (**A**) Overall survival, (**B**) cancer specific survival.

Natural history and prognostic nomogram of untreated triple negative breast cancer based on SEER database. Wang, D., Yang, Y., Rong, W. *et al.* *Sci Rep* **15**, 23347 (2025). https://doi.org/10.1038/s41598-025-07114-2

Triple-Negative Breast Cancer. N Engl J Med. November 10, 2010



Triple-Negative Breast Cancer. N Engl J Med. November 10, 2010



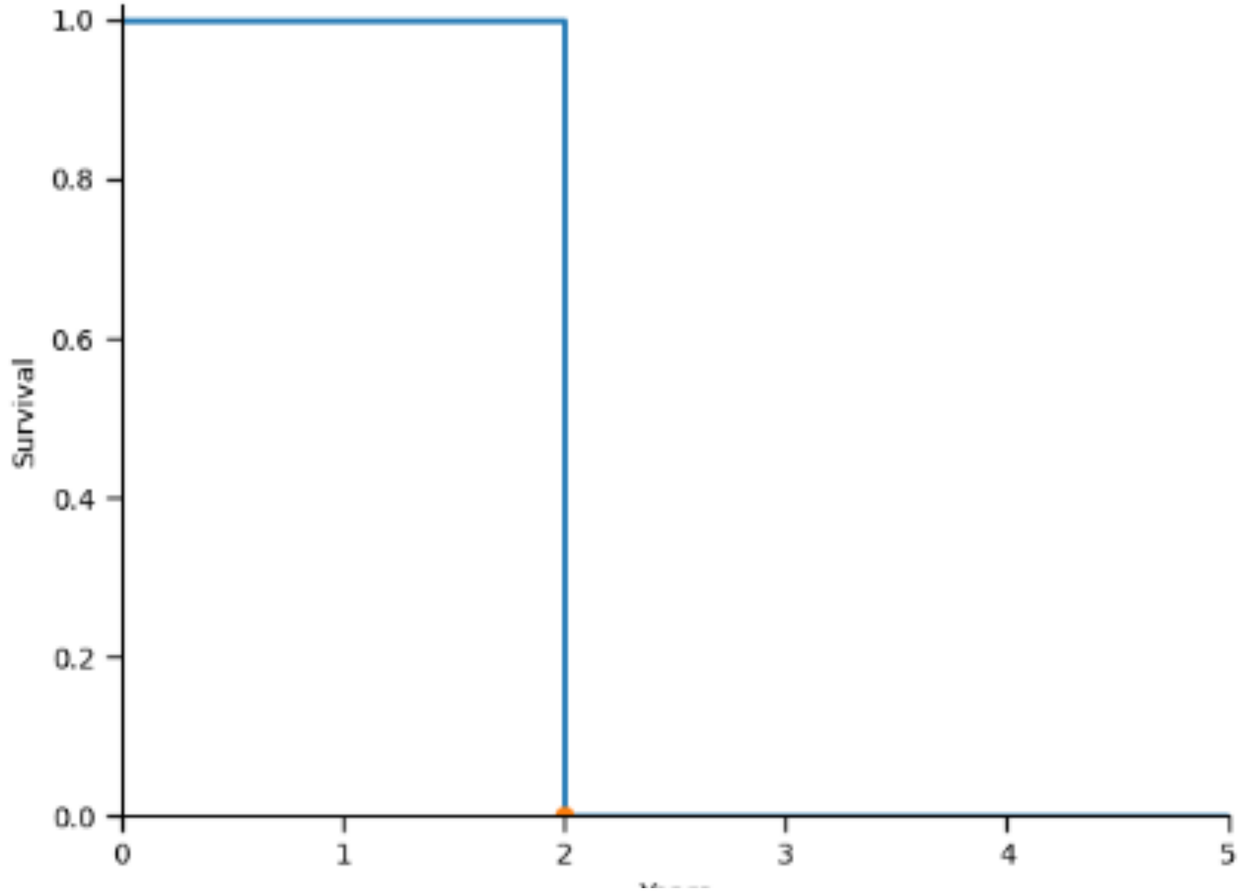
Evolution of Chemotherapy Regimens for TNBC

Era	Regimen	Key Outcomes	References
1990s	CMF, anthracycline-based (FAC/FEC)	~25-30% mortality reduction vs. no chemo	[1]
2000s	Anthracycline + Taxane (AC→T, TAC)	~33% mortality reduction; became standard of care	[2]
2010s	Addition of Platinum (carboplatin)	DFS HR 0.63-0.69; OS HR 0.69-0.70	[3-4]
2020s	Pembrolizumab + chemo (KEYNOTE-522)	3-year EFS 84.5% vs 76.8%; pCR 64.8% vs 51.2%	[5-6]
2020s	Adjuvant olaparib (BRCA-mutated)	iDFS HR 0.58; OS HR 0.68	[5, 7]

1. Platinum-Based Chemotherapy for Early Triple-Negative Breast Cancer. The Cochrane Database of Systematic Reviews. 2023. Mason SR, Willson ML, Egger SJ, et al.
2. Breast Cancer Treatment: A Review. The Journal of the American Medical Association. 2019. Waks AG, Winer EP.
3. Molecular Alterations in Triple-Negative Breast Cancer-the Road to New Treatment Strategies. Lancet. 2017. Denkert C, Liedtke C, Tutt A, von Minckwitz G.
4.Platinum Chemotherapy for Early Triple-Negative Breast Cancer.Breast. 2024. Mason SR, Willson ML, Egger SJ, et al.
5. Cancer Treatment and Survivorship Statistics, 2025. CA: A Cancer Journal for Clinicians. 2025. Wagle NS, Nogueira L, Devasia TP, et al

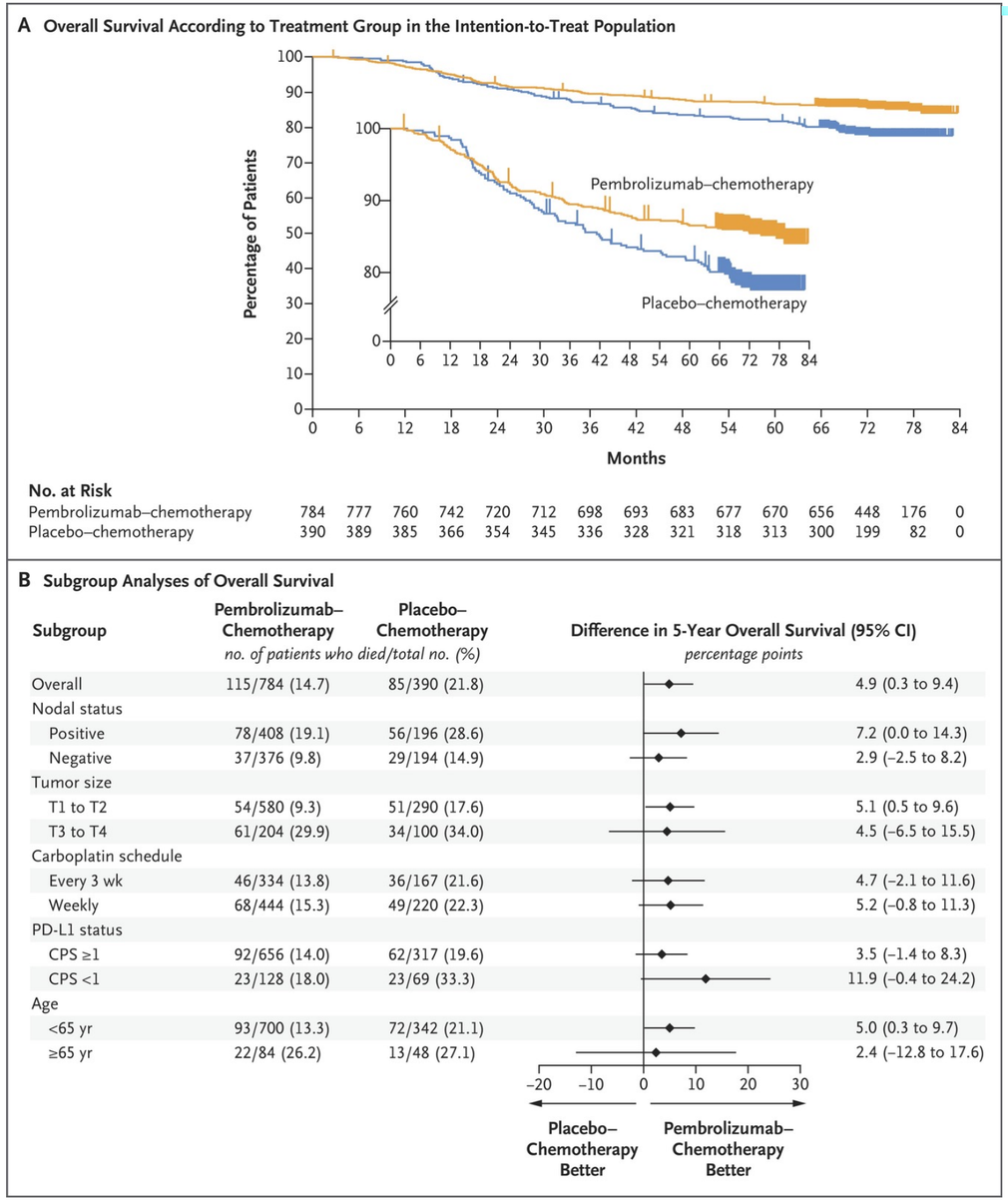
Kaplan-Meier curve, anecdotal case (n=1)

Event occurring at year 2 of intervention

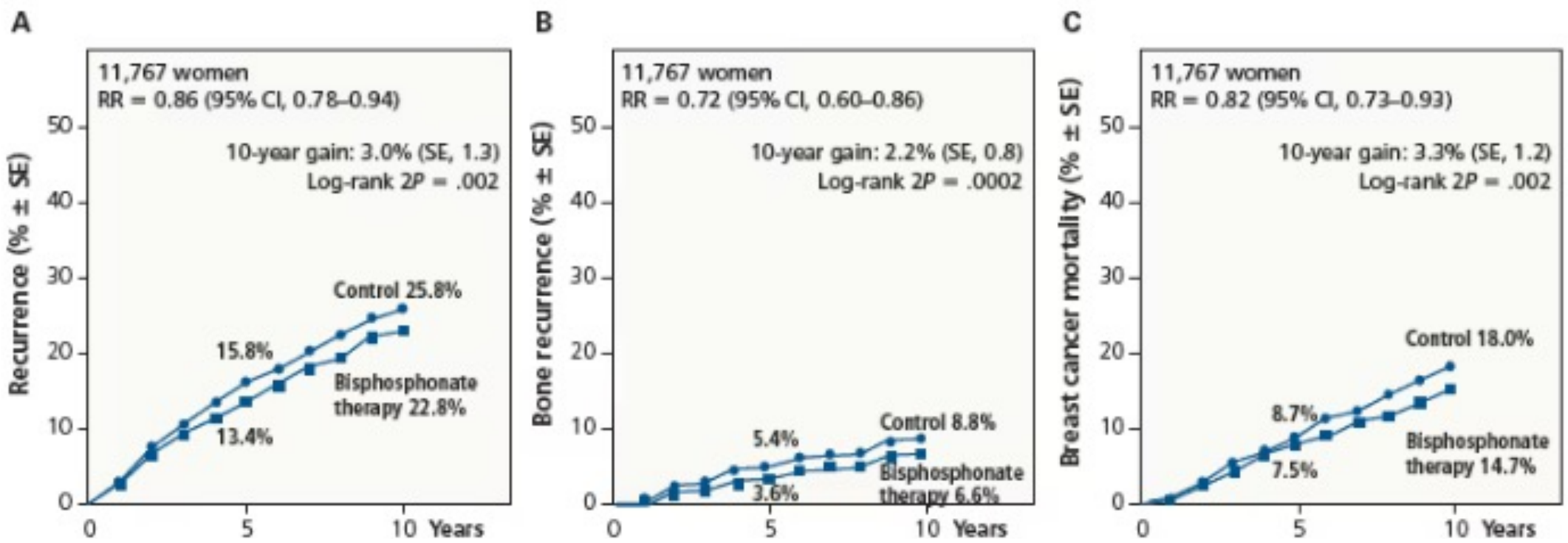


Keynote-522 study

- Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer Schmid P, Cortes J, Dent R, et al., N Engl J Med 2024;391:1981-1991 DOI: 10.1056/NEJMoa2409932



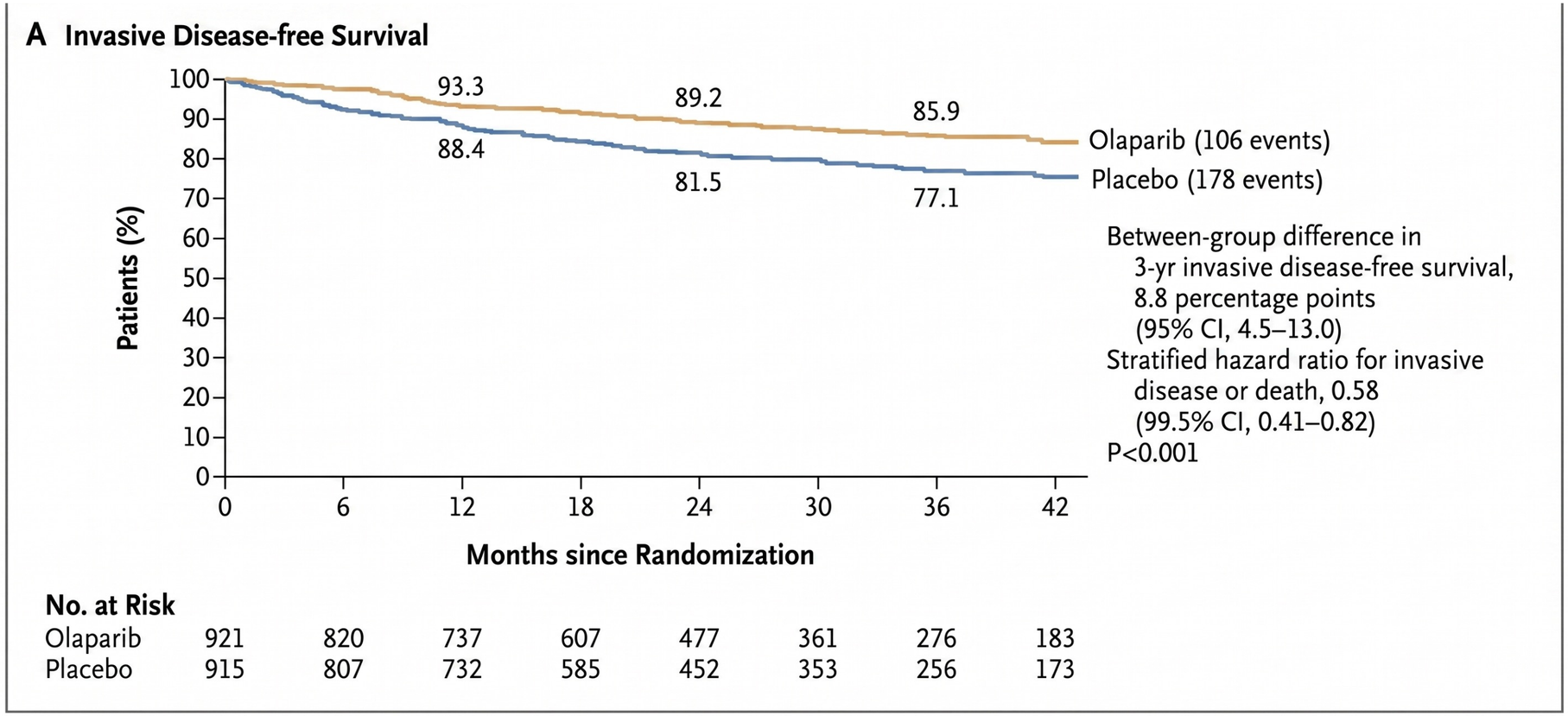
EBCTCG Meta-analysis of adjuvant bisphosphonates



Data for postmenopausal women and show **(A)** breast cancer recurrence, **(B)** bone recurrence, and **(C)** breast cancer mortality

Adjuvant Bisphosphonate Treatment in Early Breast Cancer: Meta-Analyses of Individual Patient Data From Randomised Trials. Early Breast Cancer Trialists' Collaborative Group et al. Lancet 2015. DOIL http://dx.doi.org/10.1016/S0140-6736(15)60908-4

Adjuvant Olaparib for Patients with BRCA-Mutated Breast Cancer OlympiA Trial



Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. June 23, 2021.

IT TAKES A VILLAGE:

Comprehensive services well beyond treatment to nurture the mind, body and soul of the patient

EMERGING TRENDS IN MEDICINE

Approaching a Patient with a New Cancering Process

Tumor Centric + Terrain Centric = Integrative Oncology

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Important Clinical Disclaimer

Many of the therapies discussed in this presentation are not FDA-approved for the treatment of cancer.

These interventions are presented within the context of integrative oncology.

These approaches are not intended to replace standard oncologic care, including chemotherapy, radiation, surgery, or immunotherapy.

All treatment decisions should be made in collaboration with a qualified oncology team and individualized to the patient.

Goals

Identify terrain needs for each patient and work on addressing:

- Advanced functional testing, especially in patients receiving immune checkpoint inhibitors
- How can she improve her responsiveness to standard of care treatment and lower toxicity?
- How can she maintain a long-term remission and lessen future malignancies?

“Terrain”

- Internal biological environment in which cancer develops, grows, and either progresses or regresses.

- Rather than focusing only on the tumor itself (genetics, mutations), terrain assessment evaluates the host factors that influence tumor behavior.

- This concept dates back to Claude Bernard and later Otto Warburg, emphasizing that disease depends not only on the “seed” (tumor) but also on the “soil” (host environment).


Science

Current Issue First release papers

HOME > SCIENCE > VOL. 280, NO. 5366 > LANDSCAPING THE CANCER TERRAIN

RESEARCH COMMENTARIES

Landscaping the Cancer Terrain

KENNETH W. KINZLER AND BERT VOGELSTEIN Authors Info & Affiliations

SCIENCE • 15 May 1998 • Vol 280, Issue 5366 • pp. 1036-1037 • DOI: 10.1126/science.280.5366.1036

390 348

Terrain Assessment is Paramount

Standard review of history and records	Functional Medicine Questionnaire
Deep dive into possible traumas, stressors, or other root causes	Self-care: sleep, exercise, relaxation, time outside, relationships, work environment
Toxin overview: Foods, personal care products, deodorant, water, etc.	Prior gene-based vaccines or Covid-19 infections
EMF	Single nucleotide polymorphisms (SNPs)
GI microbiome testing	Toxicity testing
Onboarding labs: LDH, homocysteine, vitamin D, full thyroid testing, copper and iron testing	Dental History

The Terrain Ten

- Genetics and Epigenetics
- Inflammation and Oxidation
- Sugar and the Ketogenic Diet
- Cancer Growth and Spread
- Carcinogens and Detoxification
- Hormones
- Microbiome
- Stress and Circadian Rhythm
- Immune Function
- Mental and Emotional Well-Being

Winters N, Kelley J. The Metabolic Approach to Cancer: Integrating Deep Nutrition, the Ketogenic Diet, and Nontoxic Bio-Individualized Therapies. White River Junction, VT: Chelsea Green Publishing; 2017.

BRCA2, Diabetes & Metabolic Risk

BRCA2 mutations and metabolic dysfunction are closely linked and may influence cancer behavior and treatment response.

↑ Diabetes Risk Post-Cancer

- ~2x higher risk within 15 years after breast cancer
- Higher in patients with BMI >25
- Likely related to treatment-induced metabolic changes

Intrinsic Metabolic Dysfunction

- BRCA2 is associated with:
  - Insulin resistance
  - Dysglycemia (even at normal weight)
- Possible mechanism: ↓ IGF-1 → impaired insulin sensitivity

Diabetes & “BRCAness”

- Hyperglycemia may ↓ BRCA1/2 expression
- Impairs DNA repair (homologous recombination)
- Creates BRCA-like phenotype without mutation

Zhang S, Yang Y, Huang S, et al. Hyperglycemia suppresses BRCA1 expression through epigenetic regulation. J Biol Chem. 2010;285(51):40400-40406. doi:10.1074/jbc.M110.170860

Insulin Signaling & Tumor Progression

Insulin is a potent growth signal in cancer biology

Clinical & Experimental Evidence

- ↓ Insulin → suppressed tumor growth (animal models)
- Insulin administration → restores tumor progression
- In insulin resistance: Chronic hyperinsulinemia sustains IR / IGF-IR signaling

Mechanism

- Activation of IR-A / IGF-IR pathways
- Drives PI3K → Akt signaling cascade
- Promotes:
  - Cell proliferation
  - Tumor progression

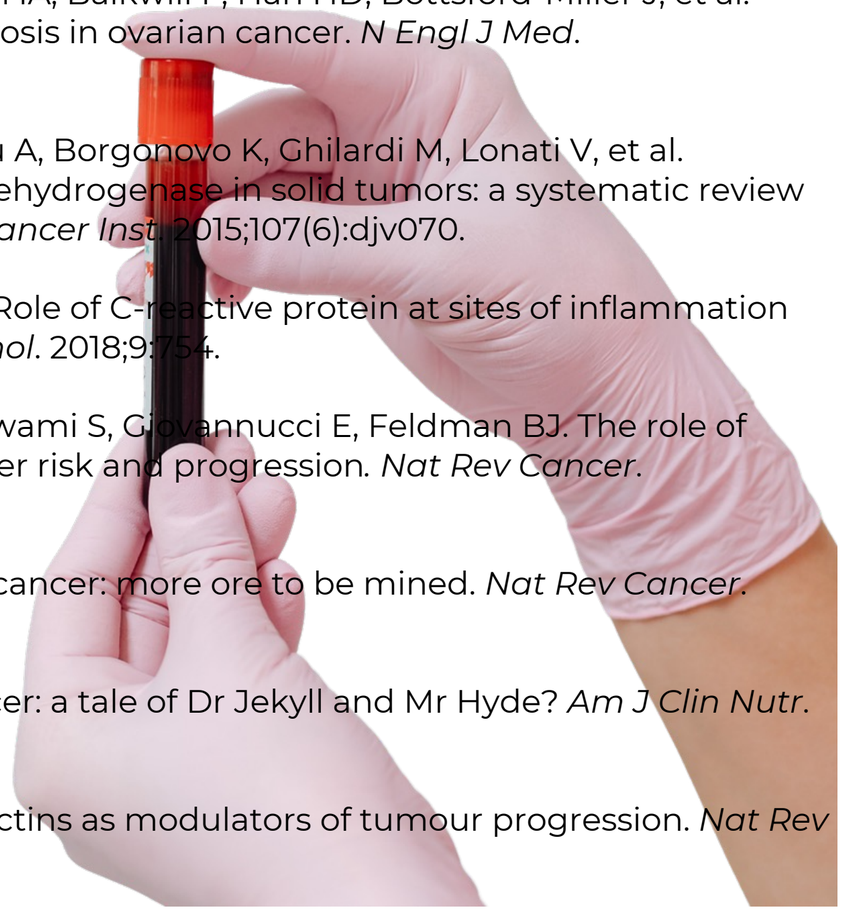
Therapeutic Implications

- Target the IR / IGF-IR / PI3K/Akt axis
- Direct inhibitors (e.g., BMS-536924)
- Metabolic therapies (e.g., metformin)

Arcidiacono B, Iiritano S, Nocera A, et al. Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. Exp Diabetes Res. 2012;2012:789174. doi:10.1155/2012/789174

Know your Labs

- Neutrophil to lymphocyte ratio
- Platelets
- Creatinine and LFTs
- LDH (isoenzymes)
- Homocysteine
- Iron stores, copper
- Galectin-3
- Full thyroid studies
- Anemia (work-up and treat thoughtfully)
- Vitamin D-25 and vitamin D 1,25
- Cardiac CRP/ESR
- Sars COV2 spike protein antibody with titer



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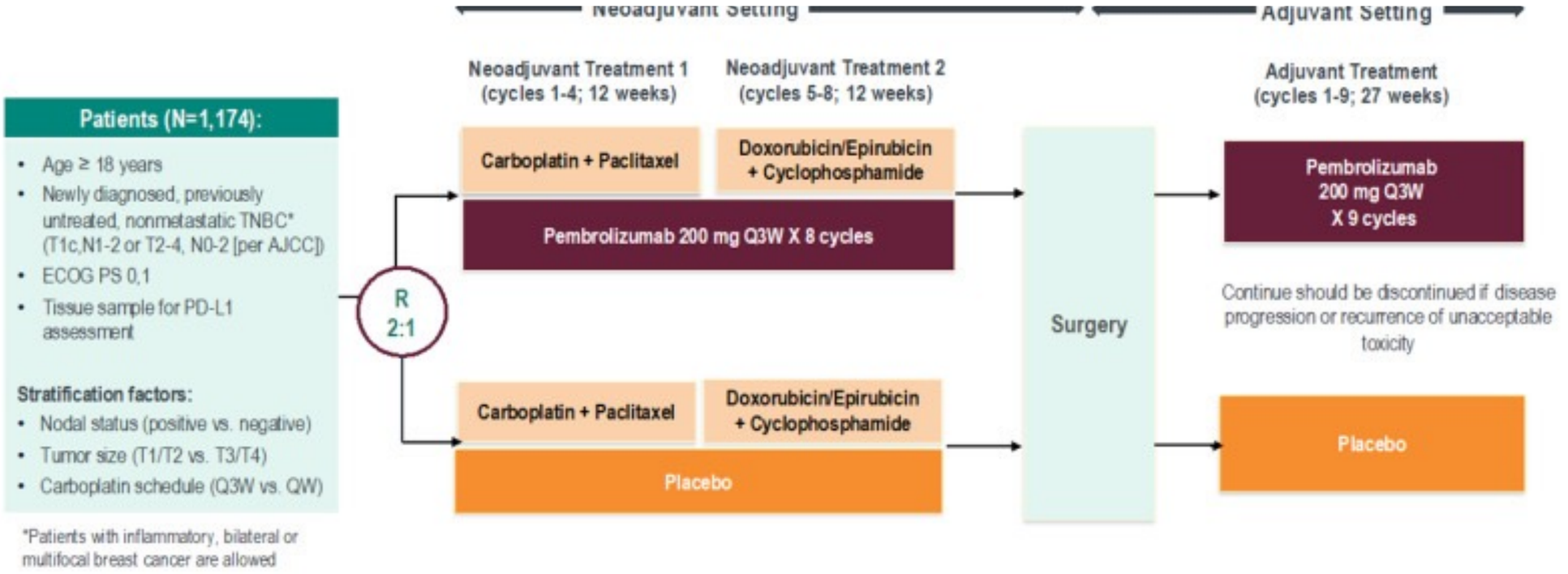
Balance:
CONVENTIONAL and ACCEPTED Treatment vs ADJUNCTIVE UNCONVENTIONAL THERAPIES

What's the Conventional Plan?



Primary Endpoints

- pCR (ypT0/Tis ypN0) assessed by local pathologist per AJCC criteria at time of definitive surgery
- EFS assessed by investigator

Secondary Endpoints

- pCR using alernative definitions (ypT0 ypN0 and ypT0/Tis)
- OS, Safety, PROs (EORTC-QLQ-C30, EORTC-QLQ-BR23, EQ-5D-5L)
- pCR (ypT0/Tis ypN0, ypT0 ypN0 and ypT0/Tis), EFS and OS in patients with PD-L1+ tumors (CPS ≥ 1%)

Wang J, Wu SG. Breast cancer: an overview of current therapeutic strategies, challenges, and perspectives. *Breast Cancer* (Dove Med Press). 2023;15:721-730

What Else Can We Do to Support the Patient?

- Address root causes
- Toxicity assessment
- Detoxification of lifestyle/self-care
- Clearing effects of "Spike protein" and post COVID (PASC) or post vaccine pathogenetic factors
- Alkalization
- Melatonin
- Avoid drugs that decrease immunotherapy responsiveness:
  - PPI, antibiotics, acetaminophen
- Fasting during treatment and anti-cancer diet
- Vitamin D3 with vitamin K2
- Magnesium
- Targeting treatment of her insulin resistance and other terrain targets
- Metformin may help mitigate insulin therapy stimulation of cancer
- Local Hyperthermia
- Gut assessment and microbiome support
- SNPs assessment
- Bio-electricity
- Long-term remission duration strategies
- Repurposed drugs
- Mistletoe
- Methylene blue with red light

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Is There Data?

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How to Lessen Her Toxicity

- Stressors, relaxation, sleep, exercise, sunlight, grounding, water supply, shower filters, real food, spices
- Fiber to improve elimination
- Fasting during treatment
- Taxol-cold capping/cryotherapy
  - Acetyl L-Carnitine and ALA
- Cardiotoxicity
  - CoQ10, L-carnitine, Hawthorne Berry
- Melatonin during treatment, including radiation

Marik PE. Cancer care: repurposed drugs and metabolic interventions in treating cancer [Internet]. Independent Medical Alliance; 2024 Oct 1 [cited 2026 Apr 11]. Available from: https://imahealth.org/research/cancer-care/
Pashaki AS, Sheida F, Shoar LM, et al. Melatonin for cancer-related fatigue in breast cancer patients: a randomized controlled trial. *Integr Cancer Ther*. 2023;22:15347354231168624.
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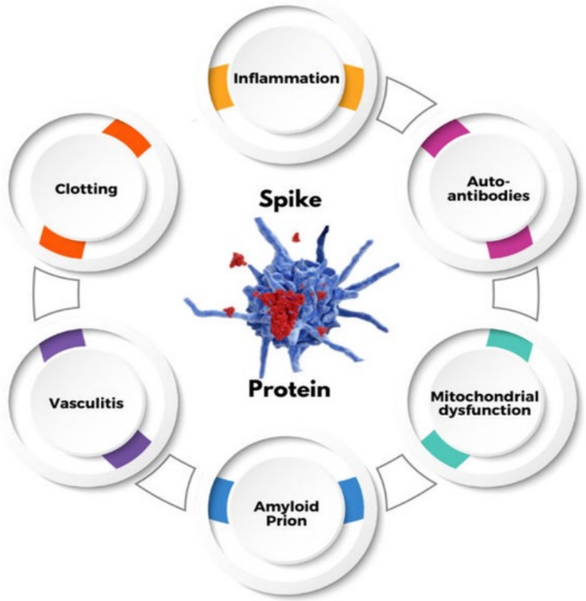
Spike protein and post COVID (PASC) or post vaccine pathogenetic factors

The spike protein of SARS-CoV-2 has extensive sequence homology with multiple endogenous human proteins and could prime the immune system toward development of both auto-inflammatory and autoimmune disease.

Figure 1. Complex pathophysiology of spike-related vaccine-induced disease



Source: IMA I-RECOVER: Post-Vaccine Treatment Protocol (2024-03-01)

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There are many references for Alternative Therapies in the Oncological literature

Many of the therapies discussed are outlined in more detail in IMA's Cancer care Monograph, which includes over 1,400 scientific references.
(Marik PE (Ed): Cancer Care: Repurposed Drugs & Metabolic Interventions in Treating Cancer. 2024); https://imahealth.org/research/cancer-care/

Specific References for key therapies:

- Melatonin: 645, 253, 646, 647
- Intermittent Fasting: 334-338
- Vitamin D3 & K: 553, 554, 555
- Metformin: 246, 247, 665, 666
- Mistletoe: 913, 914, 915-919
- Repurposed Drugs:
  - Propranolol: 154, 265, 266, 609
  - Ivermectin: 734-736, 737,
  - Mebendazole/ Fenbendazole/Albendazole: 154, 163, 231
  - Atorvastatin or Simvastatin: 676, 830, 831
  - Phosphodiesterase 5 Inhibitors: Sildenafil, Tadalafil, and Vardenafil: 262, 846-861
  - Disulfiram: 862-872
  - Doxycycline: 1008-1018

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Bardia A, Barton DL, Prokop LJ, Bauer BA, Moynihan TJ. Efficacy of complementary and alternative medicine therapies in relieving cancer pain: a systematic review. *J Clin Oncol*. 2006;24(34):5457-5464.
Horneber M, Bueschel G, Dennert G, Less D, Ritter E, Zwahlen M. How many cancer patients use complementary and alternative medicine: a systematic review and metaanalysis. *Integr Cancer Ther*. 2012;11(3):187-203.

Adjuncts

- Propranolol
- Aspirin
- Ca-D-Glucarate
- Genistein
- Consider an ivermectin/mebendazole-based protocol for high-risk patients overlapping with chemotherapy
- Gut microbiome assessment
- Nutraceuticals
- Avoid/lessen quercetin, resveratrol, and EGCG>750 mg if COMT slow
- Sulforaphane

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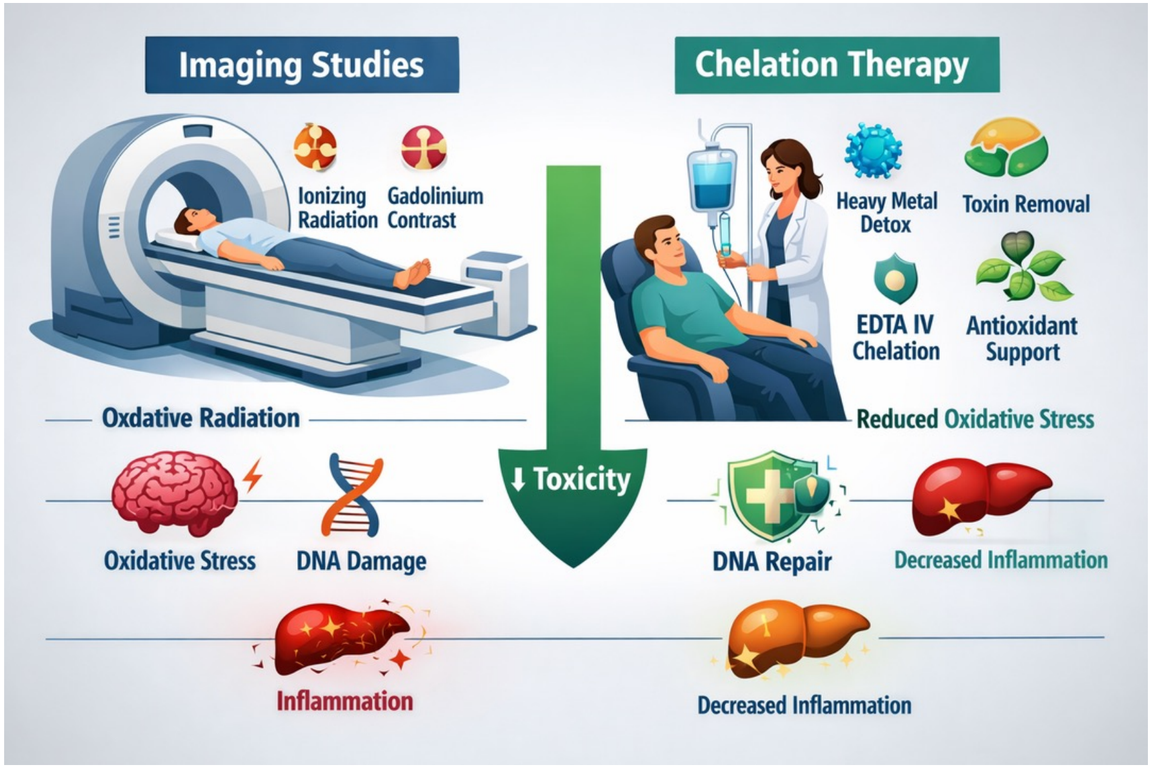
isolation and elucidation of structure. *Proc Natl Acad Sci U S A*. 1992;89(6):2399-2403.

Education

- Help her prepare for surgery or biopsies
- Help her lessen the toxicity from imaging studies and radiation
- Consider toxicity testing and possible chelation in 6-12 months (gadolinium and platinum)



Conclusions

- The patient has a pro-cancer phenotype and genotype
- Earlier integration is critical
- **The terrain must be worked on** throughout her treatment and beyond
- *Addressing her insulin resistance, inflammation, and other terrain drivers is paramount and may assist in keeping her in remission.*

Now that the oncologist has addressed her tumor based on the standard of care/NCCN guidelines, **who is going to address her pro-cancerous comorbid illness and toxic lifestyle**? These are critical determinants in maintaining a remission and whether she will develop a secondary primary malignancy.

EMERGING TRENDS IN MEDICINE

Metabolic, Hormonal, and Terrain Drivers of Aggressive Prostate Cancer

With

Dr. Jamie Waselenko

MD, FACP, FICT

Cincinnati Integrative Oncology & Functional Medicine

Goals and Take Aways

Terrain analysis (root causes) and remediation is foundational
Who is responsible to help the patient reverse his pro-cancer phenotype?

Low hanging fruit few patients and providers address

How to support the patient with biopsies, scans, ADT, chemotherapy and radiation therapy.

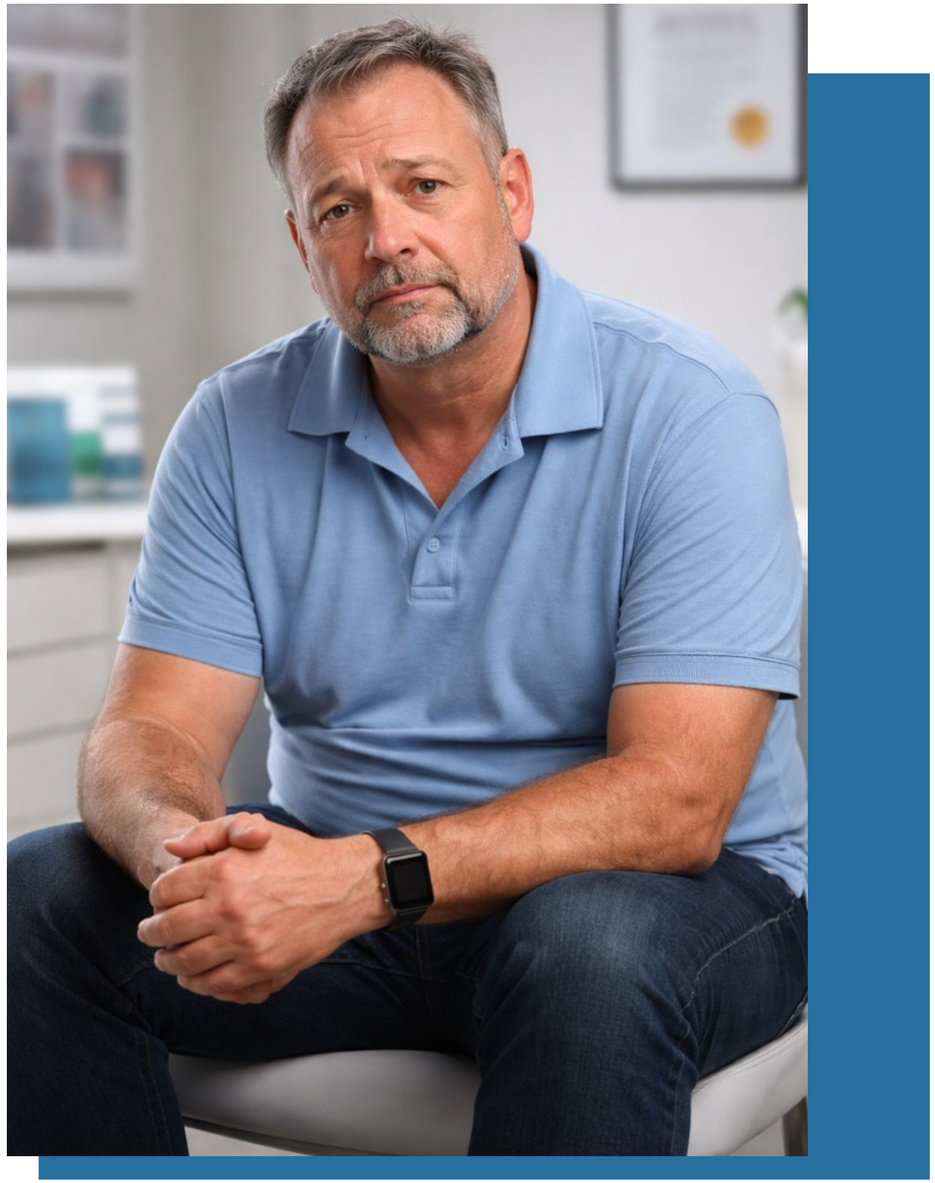
Patients often do better with integration.

Steven’s Story

56-year-old male presenting for integrative oncology consultation after declining standard-of-care treatment

“It is more important to know what sort of person has a disease than to know what sort of disease a person has.”

— Hippocrates



Steven's Story

Medical History

Past medical history

- BMI 31
- Fatty liver disease
- BPH, Kidney stones
- Hypertension
- GERD on chronic omeprazole
- Pre-diabetes
- Obstructive sleep apnea, CPAP intolerant / non-compliant
- **Medications:** lisinopril, omeprazole 40 mg po nightly for years, Tylenol 1000 mg daily for joint pain

Lifestyle and context

- Sedentary CEO
- 12-hour workdays, 6 days/week
- Sleeps ~4 hours/night with frequent awakening
- Processed-food diet since divorce 3 years earlier
- 21 eggs per week
- Three mixed drinks nightly to relax and sleep
- Chronic constipation with bowel movements about twice weekly

Additional history

- No antecedent personal or family cancer history
- Three root canals (Teeth 15, 19, and 31), 6 amalgams, wisdom teeth extracted
- Local water database notable for multiple contaminants, including high arsenic burden
- 3 Covid-19 mRNA gene based vaccines

Conventional Radiology and Pathology

Biopsy

- Poorly differentiated adenocarcinoma
- Cancer in 9/10 cores
- Gleason 9 (4 + 5)

Blood-Based Tumor Assessment

Revealed mutations in TP53, PIK3CA, ATM, ESR1, NF1, BRCA2, ARID1A, and APC. MSI-stable, Tumor mutation burden 16 mut/Mb

* No Homologous Recombination Deficiency

MRI Prostate

- PIRADS-5 lesion
- Possible neurovascular bundle invasion
- No lymph node involvement identified

PSMA Scan

- Positive L3 vertebral body lesion

Lumbar MRI

- Findings consistent with osseous metastasis at L3
- No nerve root or spinal cord compression

Clinical summary: high-grade, biologically aggressive prostate cancer with metastatic spread (oligometastatic).

(Barnett RM, Jang A, Lanka S, Fu P, Bucheit LA, Babiker H, Bryce A, Meyer HM, Choi Y, Moore C, Garje R, Gao X, Kim DW, Chang RY, Gulhati P, Ramaker R, Bansal R, Zhang T, Oliver Sartor A, Armstrong AJ, Bilen MA, Barata P. Blood-based tumor mutational burden impacts clinical outcomes of immune checkpoint inhibitor treated breast and prostate cancers. Commun Med (Lond). 2024 Dec 2;4(1):256. doi: 10.1038/s43856-024-00687-5. PMID: 39623081; PMCID: PMC11612475.)

Laboratory Findings

Inflammatory & Immune	Nutrient, Methylation & Thyroid	CBC Pattern	Hormonal	Metabolic
CRP 12 ESR 48 Ferritin 588 WBC 5.2 ANC 3.5 ALC 0.8 VEGF 141 high NLR Ratio 4.4 Spike protein Ab titer 17,100 U/ml	Vitamin D 25-OH 11 ng/mL Homocysteine 17 B12 488 Folate 11 TSH 5.3 Free T4 1.7 Free T3 1.8 Thyroid antibodies positive	Hgb 12 / Hct 36 MCV 102	PSA 28 CEA 1.3 Total testosterone 180 SHBG 153 Estradiol 52 Prolactin 17 AM cortisol 21 DHEA-S 42	Insulin 20 HbA1c 5.8% IGF-1 188 AST / ALT mildly elevated Creatinine 1.4

Standard of Care Management: High-Grade Metastatic Prostate Cancer (Gleason 9, Bone Metastasis)

- Systemic Therapy (Foundation)Androgen Deprivation Therapy (ADT) (LHRH agonist or antagonist ± antiandrogen)
- Treatment intensification (preferred):
  - Abiraterone + prednisone or
  - Enzalutamide / Apalutamide / Darolutamide
- Consider Docetaxel chemotherapy (especially high-volume or aggressive disease)
- Local & Metastasis-Directed Therapy
  - Radiation therapy to the primary prostate (improves survival in low-volume metastatic disease)
  - SBRT to oligometastatic lesions (e.g., L3 vertebra)
- Bone Health & Supportive Care
  - Zoledronic acid or Denosumab
  - Calcium + Vitamin D supplementation
  - Pain control and functional preservation
- Genomic-Directed Therapy (if progression)
  - PARP inhibitors (if HRR mutation-positive)
  - PSMA-targeted radioligand therapy (later-line)

National Comprehensive Cancer Network. Prostate Cancer (Version 4.2024). NCCN Clinical Practice Guidelines in Oncology.

Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352–360.

Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumor for newly diagnosed metastatic prostate cancer (STAMPEDE). *Lancet*. 2018;392(10162):2353–2366.

The Terrain Ten

- Genetics and Epigenetics
- Inflammation and Oxidation
- Sugar and the Ketogenic Diet
- Cancer Growth and Spread
- Carcinogens and Detoxification
- Hormones
- Microbiome
- Stress and Circadian Rhythm
- Immune Function
- Mental and Emotional Well-Being

Winters N, Kelley J. The Metabolic Approach to Cancer: Integrating Deep Nutrition, the Ketogenic Diet, and Nontoxic Bio-Individualized Therapies. White River Junction, VT: Chelsea Green Publishing; 2017.

SNPs / Genetic Terrain

Relevant polymorphisms

- CYP19A1 heterozygote
- CYP1B1 GG homozygote
- MTHFR C677T heterozygote
- MTHFR A1298C heterozygote
- MTRR AG
- COMT AA (Slow)
- PEMT CC
- VDR polymorphisms ×2
- CYP2R1 GG
- GSTO2 GG
- GSTP1 AG

Functional Implications - Investigational

- increased aromatase pressure/altered estrogen handling
- reactive estrogen metabolite burden
- impaired methylation
- Possible increased choline needs
- impaired detoxification capacity
- altered vitamin D activation and signaling
- slower catecholamine/catechol estrogen clearance in slow COMT terrain

Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med*. 2016;375(5):443–453.
Conteduca V, Wetterskog D, Sharabiani MTA, Grande E, Fernandez-Perez MP, Jayaram A, et al. Androgen receptor gene status and response to targeted therapies in advanced prostate cancer.
Ann Oncol. 2019;30(5):805–812.
Shui IM, Mucci LA, Kraft P, Tamimi RM, Lindstrom S, Penney KL, et al. Vitamin D-related genetic variation, plasma vitamin D, and risk of lethal prostate cancer. *J Natl Cancer Inst*. 2012;104(9):690–699.

Gut Digestive Function & Microbiome

Estrogen Recycling & Detoxification Burden

- Elevated β-glucuronidase increases the deconjugation of estrogens and xenobiotics
- Promotes enterohepatic recirculation → higher systemic estrogen exposure

Clinically relevant in the context of:

- CYP1B1 (↑ reactive estrogen metabolites)
- COMT variants (↓ methylation clearance capacity)

Dysbiosis, Barrier Dysfunction & Inflammation

- Low Akkermansia → reduced mucosal integrity and protective signaling
- Overgrowth of Streptococcus, Pseudomonas → pro-inflammatory microbiome shift
- Elevated zonulin → increased intestinal permeability (“leaky gut”)
- Long-term omeprazole (40 mg nightly)

Leads to:

- Systemic endotoxemia (LPS exposure)
- Chronic inflammatory signaling
- Contribution to prostate microenvironment inflammation
- Likely hypochlorhydria

Sfanos KS, Markowski MC, Peiffer LB, Ernst SE, White JR, Pienta KJ, et al. Compositional differences in gastrointestinal microbiota in prostate cancer patients treated with androgen axis-targeted therapies. *Prostate Cancer Prostatic Dis*. 2018;21(4):539–548.
Pernigoni N, Zagato E, Calcinotto A, Troiani M, Mestre RP, Calì B, et al. Commensal bacteria promote endocrine resistance in prostate cancer through androgen biosynthesis. *Science*. 2021;374(6564):216–224.
Liss MA, White JR, Goros M, Gelfond J, Leach R, Johnson-Pais T, et al. Metabolic biosynthesis pathways identified from fecal microbiome associated with prostate cancer. *Eur Urol*. 2018;74(5):575–582.

Toxic Burden Findings

Toxicity assessment notable for elevations in:

- arsenic
- cadmium
- gadolinium
- BPA
- diphenyl phosphate (DPP)
- multiple micro-toxins (trichothecenes)

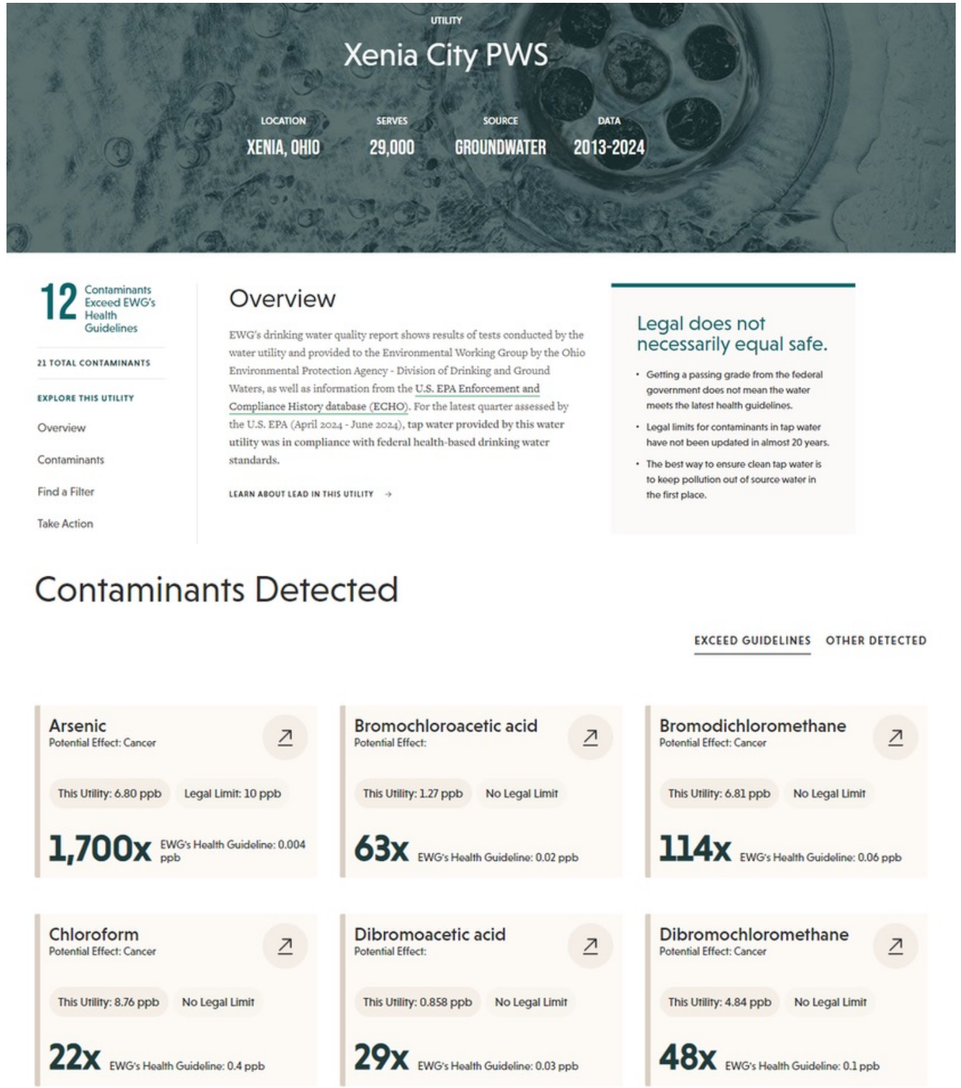
Potential biologic implications

- endocrine disruption
- mitochondrial stress
- oxidative damage
- inflammatory signaling
- impaired detoxification reserve

Additional terrain contributors (emerging)

- contaminated water exposure
- chronic pharmaceutical burden
- dental materials/procedures

Gann PH. Risk factors for prostate cancer. *Rev Urol*. 2002;4(Suppl 5):S3–S10.



Investigational Terrain-Based Intervention Targets

Treat obstructive sleep apnea

Mechanistic rationale

- reduces intermittent hypoxia
- may lower HIF-1α / VEGF signaling
- may reduce immune suppression & angiogenic drive
- CPAP significantly reduces elevated CRP & prolactin

Case relevance

- severe untreated OSA
- fragmented sleep
- elevated VEGF
- fuels metastatic disease

Restore sleep quantity and circadian rhythm

Mechanistic rationale

- improves immune coordination
- reduces inflammatory burden
- supports melatonin physiology
- reduce tumor-promoting stress signaling

Case relevance

- ~4 hours sleep nightly
- insomnia / frequent awakening
- nighttime alcohol use

Lee EJ, Suh JD, Cho JH. The incidence of prostate cancer is increased in patients with obstructive sleep apnea: Results from the national insurance claim data 2007–2014. Medicine (Baltimore). 2021;100(6):e24563.
Campos-Rodriguez F, et al. Sleep-disordered breathing and prostate cancer. *Sleep Med*. 2022;92:138–144.

Investigational Terrain-Based Intervention Targets

Prescribe structured exercise

Mechanistic rationale

- reduces insulin resistance
- improves inflammatory tone
- lowers IGF-1 signaling
- improves mood, fatigue, and metabolic flexibility
- chronic exercise may decrease prolactin

Case relevance

- sedentary
- obese
- insulin resistant
- high stress

Correct severe vitamin D deficiency

Mechanistic rationale

- supports VDR-mediated differentiation
- supports immune surveillance
- may reduce aggressive tumor biology

Case relevance

- vitamin D 11 ng/mL
- VDR / CYP2R1 SNP burden

Cassell A, Konneh S. Vitamin D in prostate cancer prevention. *World J Clin Oncol*. 2024;15(2):169–174.
Morote J, Celma A, Planas J, et al. Sedentarism and overweight as risk factors for the detection of prostate cancer and its aggressiveness. *Actas Urol Esp*. 2014;38(5):287–292.

Investigational Terrain-Based Intervention Targets

Anti-cancer / anti-inflammatory diet

Priorities

- eliminate processed foods
- avoid commercial dairy and processed meats
- remove gluten
- lower choline-heavy pattern where appropriate
- emphasize phytonutrient-rich whole foods
- Taper off PPI, adding digestive support

Mechanistic rationale

- improves insulin signaling
- reduces inflammatory signaling
- reduces estrogenic and microbiome burden

Correct constipation and gut dysbiosis

Mechanistic rationale

- lowers β-glucuronidase burden
- decreases estrogen recirculation
- reduces LPS / inflammatory exposure
- improves immune function and detoxification

Case relevance

- chronic constipation
- dysbiosis
- elevated zonulin
- elevated β-glucuronidase

Babakhanlou R, Gowin K. The impact of diet and nutrition on prostate cancer: Food for thought*? Curr Oncol Rep*. 2024;26(1):1–10.
Thomas RJ, Kenfield SA, Williams M, et al. Increasing phytochemical-rich foods and Lactobacillus probiotics in men with low-risk prostate cancer: A randomized, double-blind, placebo-controlled trial. *Eur Urol*. 2026;79(2):243–252.

Investigational Terrain-Based Intervention Targets

Reduce / eliminate alcohol

Mechanistic rationale

- lowers aromatase stimulation
- lowers oxidative stress
- improves sleep architecture
- reduces inflammatory and signaling
- may lower prolactin

estrogenic

Case relevance

- three mixed drinks nightly
- elevated estradiol
- poor sleep
- elevated prolactin
- Egg, choline, rich diet

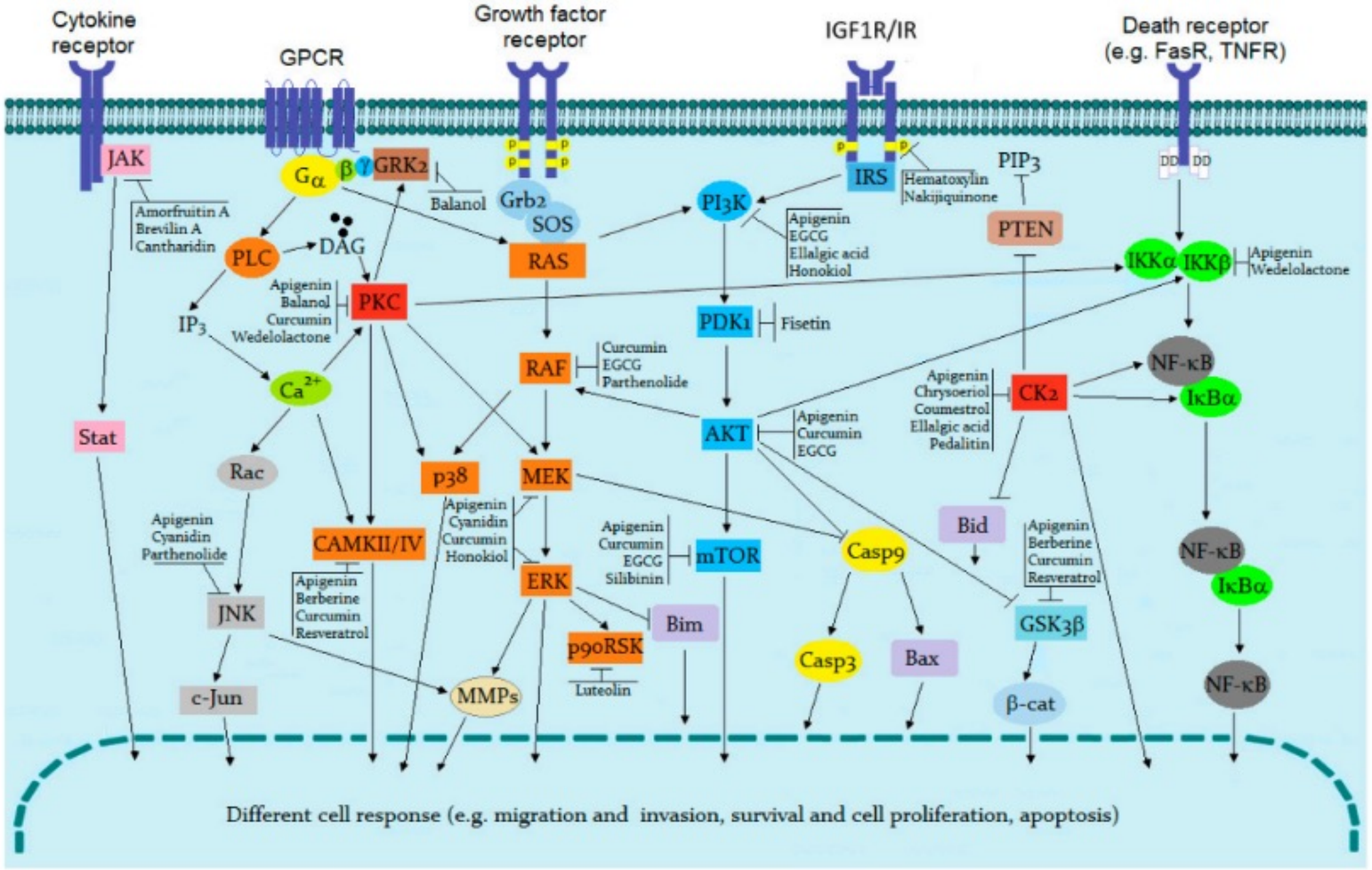
Treat co-morbidities that feed tumor biology

Examples

- OSA
- pre-diabetes / insulin resistance
- thyroid dysfunction
- chronic acid suppression / hypochlorhydria
- fatty liver disease
- toxic pro-inflammatory lifestyle
- gut dysbiosis, maldigestion
- estrogen metabolism
- elevated Prolactin
- toxins and toxic lifestyle

D'Ecclesiis O, Pastore E, Gandini S, et al. Association between alcohol intake and prostate cancer mortality and survival. *Cancers* (Basel). 2023;15(4):1187.

Intracellular transduction pathways, including protein kinases, and examples of their inhibition by natural compounds.



Baier A, Szyszka R. Compounds from natural sources as protein kinase inhibitors. *Biomoleculles*. 2020;10(11):1546. doi:10.3390/biom10111546.

Other Potential Considerations

Prostate Cancer

- Doxycycline
- EGCG and matcha tea
- Ivermectin (start at 0.8 mg/kg and increase as tolerated)
- Sulforaphane
- Curcumin
- Metformin
- Modified citrus pectin (PectaSol 14.4 g/day; six capsules three times a day)
- Vitamin D (aim for a vitamin D level of 100–150 ng/mL) + Vitamin K2
- Mebendazole
- Propranolol (10–40 mg twice daily as tolerated)
- Resveratrol
- Lycopene 15-20 mg twice daily
- Berberine
- Aged garlic extract
- Zinc (15 mg; dose <20 mg) for nonmetastatic disease; see caution below
- Quercetin (synergizes with EGCG)

In poor responders, consider:

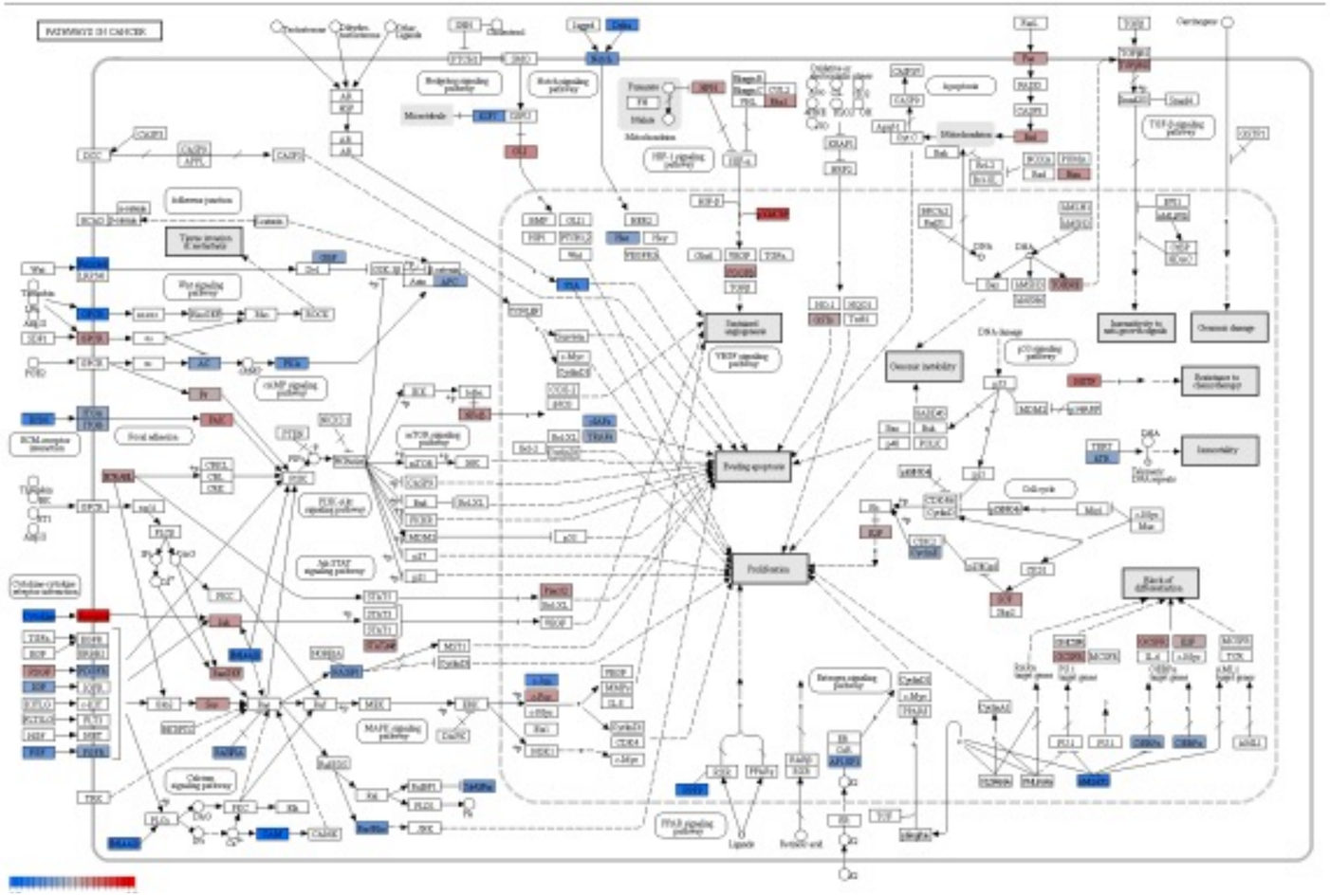
- Atorvastatin (40–80 mg daily) or simvastatin (40 mg daily)
- Aspirin (325 mg daily)
- Ketone supplements

In addition to PSA, the following blood tests are suggested HbA1C, Vitamin D, Calcium and PTH as well as total and free testosterone. Consider licorice root exact in patients with high free testosterone.

Approach to the Use of Repurposed Drugs in Patients with Cancer (01/26/2026)

Marik PE. Cancer care: repurposed drugs and metabolic interventions in treating cancer [Internet]. Independent Medical Alliance; 2024 Oct 1 [cited 2026 Apr 11].
Available from: https://imahealth.org/research/cancer-care/.

Emerging: Natural Therapy Sensitivity Testing with AI



REPORT HIGHLIGHTS	
Indications	Drugs with Benefits
GPX1 Overexpression	☑ Alpha-Lipoic Acid, Colloidal Silver, Selenomethionine
TP53 p.R196*	☑ Hydroxychloroquine, Statins, Withania somnifera
JAK2 Overexpression	☑ Artesunate, Genistein
TUBB1 Overexpression	☑ Fenbendazole, Mebendazole
HMGB1 Overexpression TP53 p.R196*	☑ Chloroquine
CD36 Overexpression	☑ Atorvastatin
ATP1A1 Overexpression	☑ Asimina triloba
ARG2 Overexpression	☑ L-Arginine

Chemosensitivity Analysis on CTCs

Chemosensitivity

Chemosensitivity assay performed on cultured circulating tumor and its associated cells indicates the effectiveness of drugs in descending order of efficacy.

Drug Names	% Cell Death	Drug Response
Resveratrol	49	
Artesunate	48	
Glibenclamide	47	
Valproic acid	46	
Metformin	45	
Iscador P	44	
Niclosamide	44	
Helixor A	43	
Chloroquine	42	
Doxycycline	41	
Fenbendazole	40	
Pantoprazole	39	
Vitamin C	38	
Dichloroacetate	36	
Epigallocatechin gallate	36	
Calcitriol	35	
Genistein	35	
Cannabidiol	34	
Hydroxy Itraconazole	33	
Quercetin	33	

Investigational Integrative Therapeutic Strategies

Rotating repurposed-drug framework

Month 1

- atorvastatin
- doxycycline
- liposomal vitamin C
- celecoxib
- dipyridamole

Month 2

- niclosamide
- aspirin
- alpha-lipoic acid
- hydroxychloroquine

Month 3

- artemisinin
- glibenclamide
- celecoxib
- Boswellia phytosome
- itraconazole

Continuous therapies

- propranolol
- low-dose naltrexone
- oral ivermectin
- mebendazole
- metformin
- melatonin
- vitamin D3 / K2
- genistein
- calcium-D-glucarate
- probiotics
- magnesium
- zinc
- modified citrus pectin
- berberine
- curcumin
- lactoferrin
- turkey tail
- Zyflamend
- black seed oil
- olive leaf extract
- lycopene
- broccoli support
- pancreatic enzymes
- bicarbonate
- ozone suppositories

Marik PE. Cancer care: repurposed drugs and metabolic interventions in treating cancer [Internet]. Independent Medical Alliance; 2024 Oct 1 [cited 2026 Apr 11].
Available from: https://imahealth.org/research/cancer-care/.

Reiter RJ, Chuffa LGA, Simão VA, et al. Melatonin and vitamin D as potential synergistic adjuvants for cancer therapy. *Int J Oncol*. 2024;65:114

Investigational Integrative Therapeutic Strategies

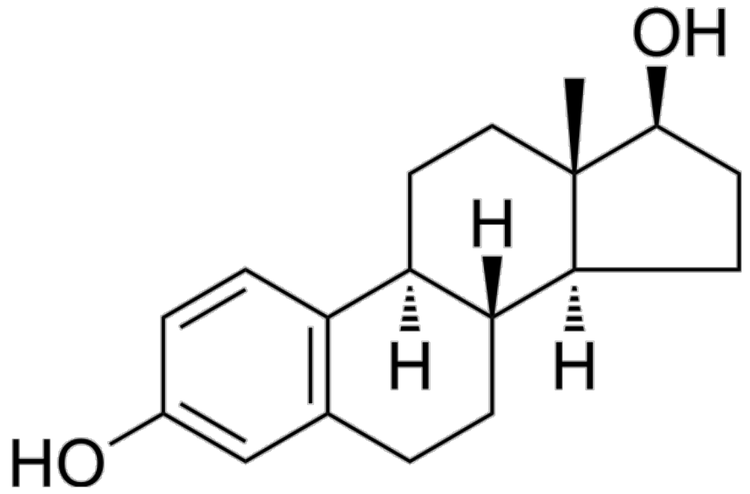
Targeting Estradiol

Why estradiol matters in this case

- obesity increases aromatase activity
- Adipose and prostate tissue can generate estrogen locally
- Estradiol was elevated at 52
- CYP19A1 and CYP1B1 terrain increases concern for estrogenic signaling and reactive estrogen metabolites
- Alcohol is an aromatase inducer
- Affects prolactin level

Therapeutic logic

- reduce adiposity/insulin resistance
- lower alcohol exposure
- improve bowel transit and lower β-glucuronidase
- support estrogen clearance
- consider calcium-D-glucarate
- use cruciferous / broccoli support judiciously
- use genistein/phytonutrient strategies thoughtfully
- avoid agents poorly tolerated in slow COMT terrain when relevant



Rahman HP, Foster PA, Kallifatidis G, et al. How oestrogen metabolism impacts prostate cancer. Endocr Relat Cancer. 2016.

Foods With Aromatase-Inhibiting Qualities

Cruciferous vegetables
- Broccoli
- Broccoli sprouts
- Brussels sprouts
- Cauliflower
- Kale
- Cabbage

Polyphenol-rich foods
- Berries
- Pomegranate
- Grapes/resveratrol-containing foods
- Apples

Phytonutrient-rich plant foods
- White button mushrooms
- Onions
- Garlic

Flavonoid-rich foods
- Green tea
- Citrus fruits

Phytoestrogen/lignan sources
- Flaxseeds
- Sesame seeds

Other foods with supportive evidence
- Turmeric (curcumin)
- Parsley
- Celery

Investigational Integrative Therapeutic Strategies

Melatonin as an Aromatase Inhibitor

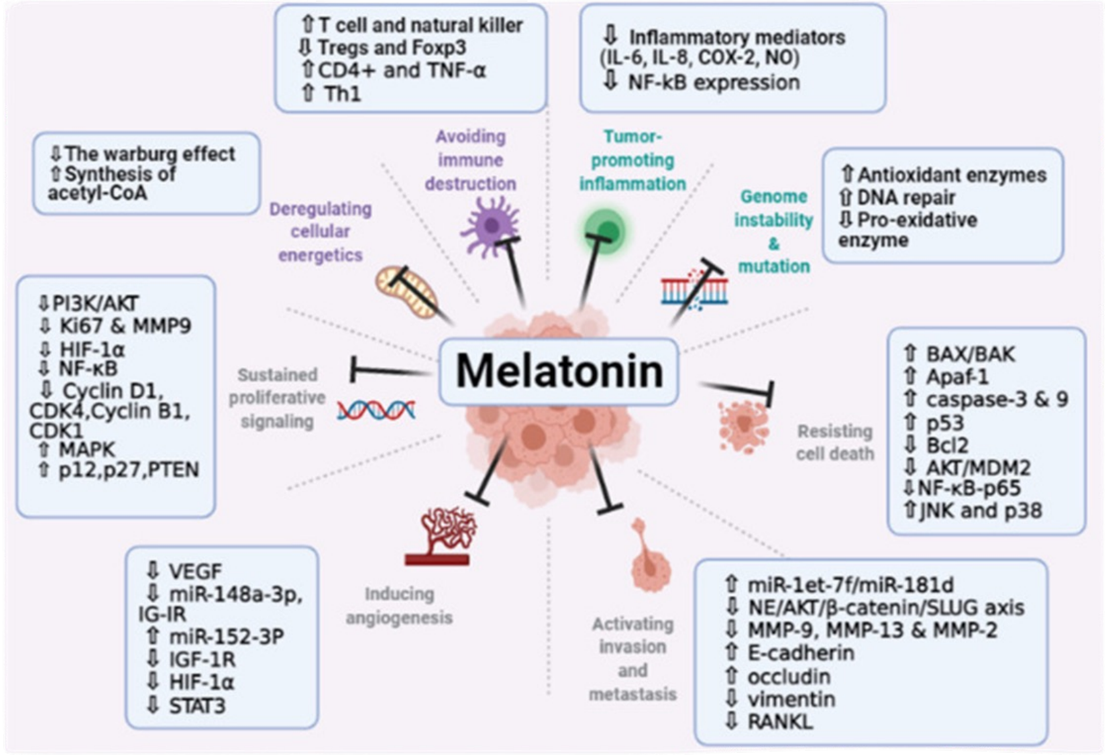
Aromatase converts androgens into estrogens, increasing estradiol levels that may contribute to tumor-promoting hormonal signaling.

Emerging research suggests melatonin may function as a natural aromatase inhibitor by:

- suppressing aromatase gene expression (CYP19A1)
- reducing aromatase enzymatic activity
- interfering with estrogen receptor signaling
- modulating estrogen-related tumor growth pathways

Case relevance

- obesity and adipose tissue aromatase expression
- chronic alcohol exposure
- inflammatory signaling
- CYP19A1 genetic terrain
- Estradiol elevation



González A, Martínez-Campa C, Mediavilla MD, Alonso-González C, Sánchez-Barceló EJ, Cos S. Inhibitory effects of pharmacological doses of melatonin on aromatase activity and expression in rat glioma cells. Br J Cancer. 2007 Sep 17;97(6):755-60. doi: 10.1038/sj.bjc.6603935. Epub 2007 Aug 14. PMID: 17700567; PMCID: PMC2360391.

Investigational Integrative Therapeutic Strategies

Targeting Prolactin

Why prolactin is relevant (emerging)

- Prolactin receptor signaling can activate STAT5B / MAPK pathways
- These pathways are associated with proliferation, migration, and aggressive behavior in prostate models
- Prolactin in this patient is clinically important and serves as a potential treatment target, often neglected
- Prolactin can stimulate prostate cancer cell growth even when androgen signaling is suppressed

Therapeutic logic

- Support sleep and circadian rhythm regulation
- Reduce alcohol exposure
- Consider dopaminergic / prolactin-lowering strategies
- Address estrogenic signaling that may influence pituitary–hormonal pathways
- Use nutrients that support dopaminergic tone: vitamin B6 (P5P), magnesium, zinc, and chaste vitex berry
- Consider how methylene blue and other pathway-modulating therapies may intersect with prolactin signaling

Agarwal N, et al. Prolactin receptor antagonist in metastatic breast and CRPC. Oncologist. 2016;21(5):535–536.
Standing D, et al. Prolactin receptor signaling as a cancer target. Front Endocrinol (Lausanne). 2022;13:1112987.

Investigational Integrative Therapeutic Strategies

Choline Restriction & Alcohol Reduction

Choline and Prostate Cancer

Emerging data suggests that high dietary choline intake may be associated with increased risk of aggressive prostate cancer and progression.

Potential mechanisms include:

- conversion of choline to TMAO by gut microbiota, which may promote inflammation and tumor progression
- increased phosphatidylcholine availability, supporting membrane synthesis in rapidly dividing cells
- altered methylation dynamics in patients with PEMT polymorphisms

Case relevance

- PEMT CC genotype affecting endogenous choline synthesis
- dysbiotic microbiome with altered metabolite signaling
- aggressive tumor phenotype

Adopt a plant-forward, phytonutrient-rich dietary pattern while limiting egg yolks, or other high-choline animal products, processed meats, and commercial dairy.

Richman EL, Kenfield SA, Stampfer MJ, et al. Choline intake and risk of lethal prostate cancer: Incidence and survival. J Natl Cancer Inst. 2012;104(14):1093–1101.

Conventional Oncology Discussion Required

Conventional approaches are the Standard of Care.
There is a suggestion of potential for improved long-term remission duration and overall survival with aggressive treatment of the primary and oligometastatic disease.

Early conventional treatment can prevent progression to castration-resistant or metastatic disease.

Patients often do better with integration.

Many metabolic, hormonal, and immune strategies can support outcomes, reduce toxicity, improve resilience and likely long-term outcomes when paired with conventional treatment.

Thinking Outside the Box

hyperthermia

mistletoe

detoxification

immune modulation

exercise

targeting co-morbidities

melatonin

IV nutraceuticals

water filtration

anti-cancer diet

sleep

community

ozone therapy

reduce insulin resistance

gut microbiome

stress reduction

alkalization

anti-toxin lifestyle

targeting pathways

bioelectricity

epigenetics

EMF limitation

anti-inflammatory lifestyle

faith

repurposed drugs

anti-cancer foods

pancreatic enzymes

methylene blue and red light

tapering off PPIs

dental contributions

IV vitamin C

supplements

Goals and Take aways

Terrain analysis (root causes) and remediation is foundational

-Who is responsible to help guide the patient in reversing his pro-cancer phenotype

Low Hanging Fruit

-Fasting, basic terrain work, melatonin, Vitamin D3/K2, magnesium

-Diet, alcohol

-Self-care, OSA

-Basic support/root protocols and consideration for repurposed drugs

-Detoxification

How to support the patient with biopsies, scans, ADT, chemotherapy and radiation therapy (standard of care therapies)

Patients often do better with integration.

IMA 2026

EMERGING TRENDS IN MEDICINE

Approach to Prostate Cancer Case Review

Dr. Ray Page
DO, PhD, FACOI, FASCO

The Center TX
Center for Cancer and Blood Disorders

Where do we go from here?

- 56-year old man, not healthy
- Doesn’t trust healthcare
- Gleason 9, Prostate adenocarcinoma, presenting PSA 28
- Oligometastatic castration-sensitive prostate cancer (mCSPC)
  - Synchronous (de novo), not metachronous (recurrent)
  - PSMA PET Isolated L3 metastasis
  - NGS mutations in TP53, PIK3CA, ATM, ESR1, NF1, BRCA2, ARID1A, and APC. MSI-stable, Tumor mutation burden 16 mut/Mb
  - Homologous Recombination Deficiency status?

- What to do?

What to do?

- **Quickly gain trust** (otherwise you are not even getting to first base)
  - Cannot tell him “he must” do this or do that
  - You must give him choice, based on shared decision-making
- **Knowledge dispels Fear!**
  - You must share knowledge with data and stats that you know cold
  - You must be able to discuss with him prognosis, anticipated responses, estimated duration of response
  - You must disclose anticipated risks, benefits, side effect and toxicities of interventions and therapies
  - You must offer flexibility (there is no emergency here)

SPIKES Protocol to deliver difficult information

- **S - Setting:** Arrange privacy, sit down, make a connection, and manage interruptions
- **P - Perception:** Determine what the patient already knows or suspects about their condition
- **I - Invitation:** Ask the patient if they are ready or wish to know the details of the diagnosis/prognosis
- **K - Knowledge:** Share the medical facts in small, understandable chunks, avoiding jargon
- **E - Emotions & Empathy:** Respond to the patient's reactions with empathy, validating their feelings
- **S - Strategy & Summary:** Create a clear plan for next steps and summarize the discussion.

SPIKES-A six-step protocol for delivering bad news: application to the patient with cancer. W F Baile, R Buckman, R Lenzi, G Glober, E A Beale, A P Kudelka, Oncologist2000;5(4):302-11. doi: 10.1634/theoncologist.5-4-302

Treatment Considerations

- **Androgen Deprivation Therapy (ADT)**
  - Luteinizing Hormone-Releasing Hormone (LHRH) agonists – many different injectables
  - Relugolix – **only ORAL Gonadotropin-Releasing Hormone (GnRH antagonist)**, directly blocking LHRH receptor

- **Androgen receptor pathway inhibitor**
  - Primarily Include daily oral Abiraterone, Enzalutamide, Apalutamide, Darolutamide

- **Radiation therapy to treat primary tumor**

- **Metastasis-directed therapy (MDT)**
  - Typically Stereotactic body radiation therapy (SBRT)

- **Bone Health Management** – Consideration of antiresorptive therapy with a Bisphosphonate or an RANKL Inhibitor to reduce fracture risk and manage bone metastases

What do we get out of this treatment???

- A virtual 100% response
- Testosterone rapidly declines to castrate levels
- PSA rapidly declines to almost undetectable levels
- Median progression free survival, typically 2 -5 years
- SBRT doubles radiographic Progression Free Survival (PFS) from 2.3 to 4.6 years (PCS-9 study)*

- Can we achieve good outcomes with Intermittent Androgen Blockade?
  - Yes! Combined XRT + intermittent hormonal can EXTEND eugonadal PFS

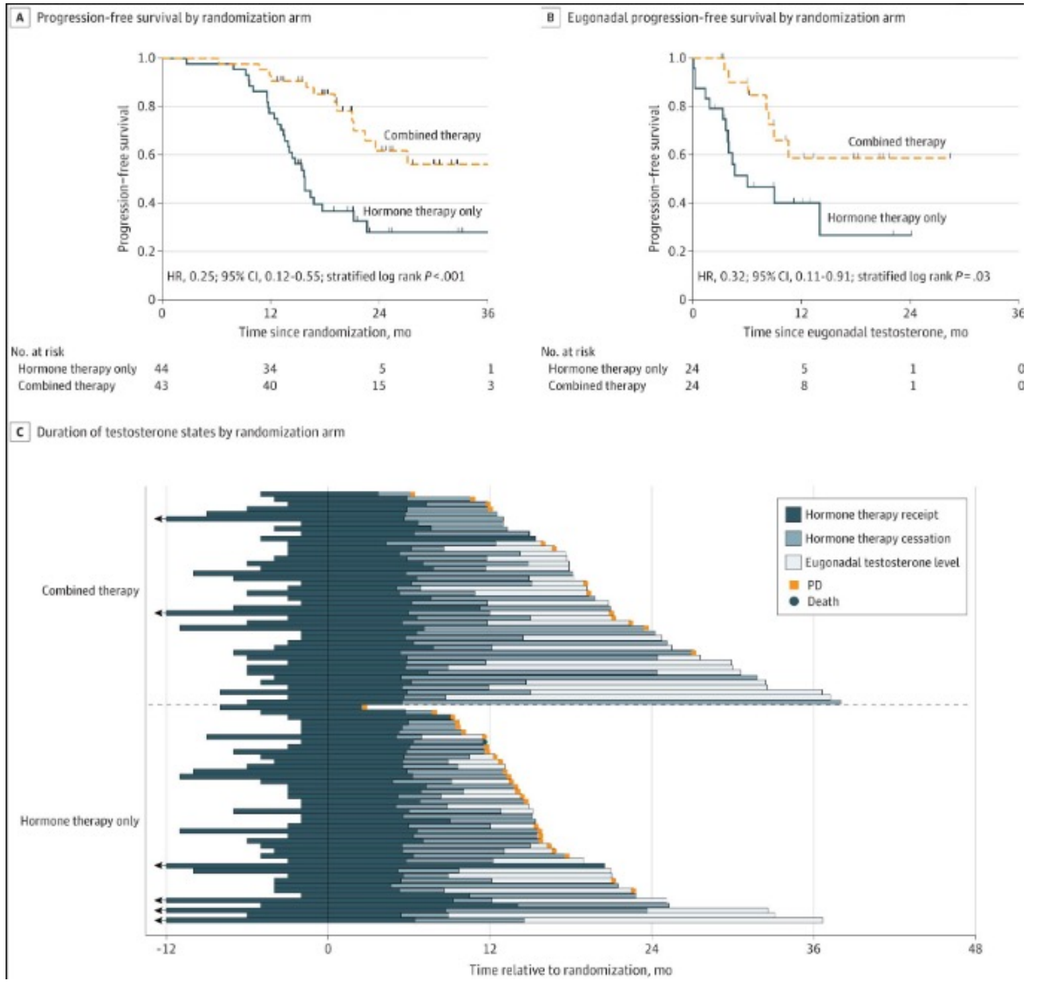
*Metastases-directed therapy in addition to standard systemic therapy in oligometastatic castration-resistant prostate cancer in Canada (GROUQ-PCS 9): a multicentre, open-label, randomised, phase 2 trial, Tamim Niazi et al., Lancet Oncol
. 2025 Sep;26(9):1158-1167. doi: 10.1016/S1470-2045(25)00351-1.

EXTEND Study

- Addition of Metastasis-Directed Therapy to Intermittent Hormone Therapy for Oligometastatic Prostate Cancer: The EXTEND Phase 2 Randomized Clinical Trial.

Tang C, Sherry AD, Haymaker C, et al.

JAMA Oncology. 2023; 9;(6):825-834. doi:10.1001/jamaoncol.2023.016



Castrate Resistant Prostate Cancer (CRPC) Treatment

- So what next, when metastatic progression of disease after the 2-5 years of hormonal treatment?
- Well, it depends, and it is nuanced based on burden of disease, prior therapies, symptoms, age/comorbidities, and molecular characteristics
- Need to do **NGS testing** on blood for ctDNA and **HRR** (homologous recombinant repair) testing for possible targetable mutations
- Considerations of treatments:
- Combined Androgen Blockade (**ADT + ARPI**) to keep castrate levels of testosterone
- **Docetaxel** chemo; **Cabazitaxel** with progression
  - STAMPEDE and CHAARTED trials showed adding Docetaxel to ADT extends survival by over a year compared to ADT alone in 1st line CSPC
  - Docetaxel + ARPI: OS 20.4m vs 13.6m*
- If BRCA mutation: add **oral PARP inhibitor** (there are a few) – Prolong OS 4.4 mo.

Translating Clinical Trials to Clinical Practice: Outcomes of Men With Metastatic Castration Resistant Prostate Cancer Treated With Docetaxel and Prednisone in and Out of Clinical Trials. Templeton AJ, Vera-Badillo FE, Wang L, et al, Annals of Oncology : Official Journal of the European Society for Medical Oncology. 2013.

Castrate Resistant Prostate Cancer (CRPC) Treatment: Further Considerations

- Radiopharmaceutical Therapy
  - **Radium-223** IV radiation for symptomatic bone only mets + zolendronic acid
  - **Lu-177 vipivotide tetraxetan-PSMA-617** for PSMA positive disease who has prior ARPI therapy, can now be given if chemo desired to be delayed. Given every 6 weeks up to 6 doses. PFS 8.7 mo vs 3.4 mo, OS 15.3 vs 11.3 mo
  - **Sipuleucel-T** therapy for asymptomatic patients without visceral disease
  - 3 doses at 2 week intervals preceded by leukapheresis 3d prior, median OS 25.8 mo, with 4.1 mo survival improvement
- **Pembrolizumab** immunotherapy, tumor-agnostic indication for MSI-High/dMMR tumors: Robust activity for this uncommon group with durable responses. 40% patient have 50% or greater decline in PSA.
- Participation in clinical trials
  - **Next-Generation Radiopharmaceuticals**
  - **Novel Antibody-Drug Conjugates**
  - **Bispecific T-cell engagers and Immunotherapy**

Thank you

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