Tumor Dormancy

Ospedaletto di Pescantina, 25 marzo 2023

P Pronzato

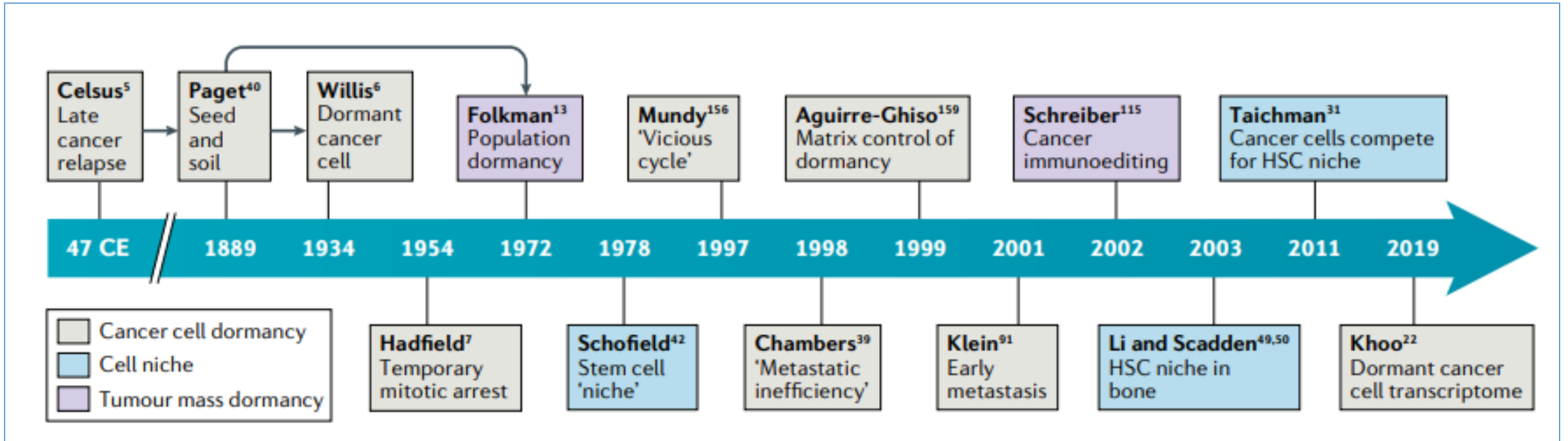# Conflict of Interests

- **Compensations for lectures (last two years)**
  - AMGEN
  - CELGENE
  - LILLY
  - MSD
  - NOVARTIS
  - ROCHE

- **Compensations for participation in advisory boards (last two yeasrs)**
  - AMGEN
  - LILLY
  - NOVARTIS
  - PIERRE FABRE
  - PFIZER
  - ROCHE

Agenda

- **Introduction**
- **Biological Bases**
- **Clinical Relevance**
- **Research and Trials**

Introduction

Timeline legend:
- Cancer cell dormancy
- Cell niche
- Tumour mass dormancy

Timeline entries (above axis):

- **Celsus[5]** — Late cancer relapse
- **Paget[40]** — Seed and soil
- **Willis[6]** — Dormant cancer cell
- **Folkman[13]** — Population dormancy
- **Mundy[156]** — 'Vicious cycle'
- **Aguirre-Ghiso[159]** — Matrix control of dormancy
- **Schreiber[115]** — Cancer immunoediting
- **Taichman[31]** — Cancer cells compete for HSC niche

Timeline axis: 47 CE — 1889 — 1934 — 1954 — 1972 — 1978 — 1997 — 1998 — 1999 — 2001 — 2002 — 2003 — 2011 — 2019

Timeline entries (below axis):

- **Hadfield[7]** — Temporary mitotic arrest
- **Schofield[42]** — Stem cell 'niche'
- **Chambers[39]** — 'Metastatic inefficiency'
- **Klein[91]** — Early metastasis
- **Li and Scadden[49,50]** — HSC niche in bone
- **Khoo[22]** — Dormant cancer cell transcriptome

TG Phan , Nat Rev Cancer 2020

Premise (Confusion)

- **Dormant Cells**
- **Stem Cells**
- **CTC**
- **DTC**

- **Habit**
- **Niche**

Biological Bases

Fate of Cancer Cells after Extravasation

- **Killing of Large Numbers because of unfavourable conditions**

- **Rapid Cell Divisions**

- Surviving and Entering a Nonproliferative State (Dormancy)
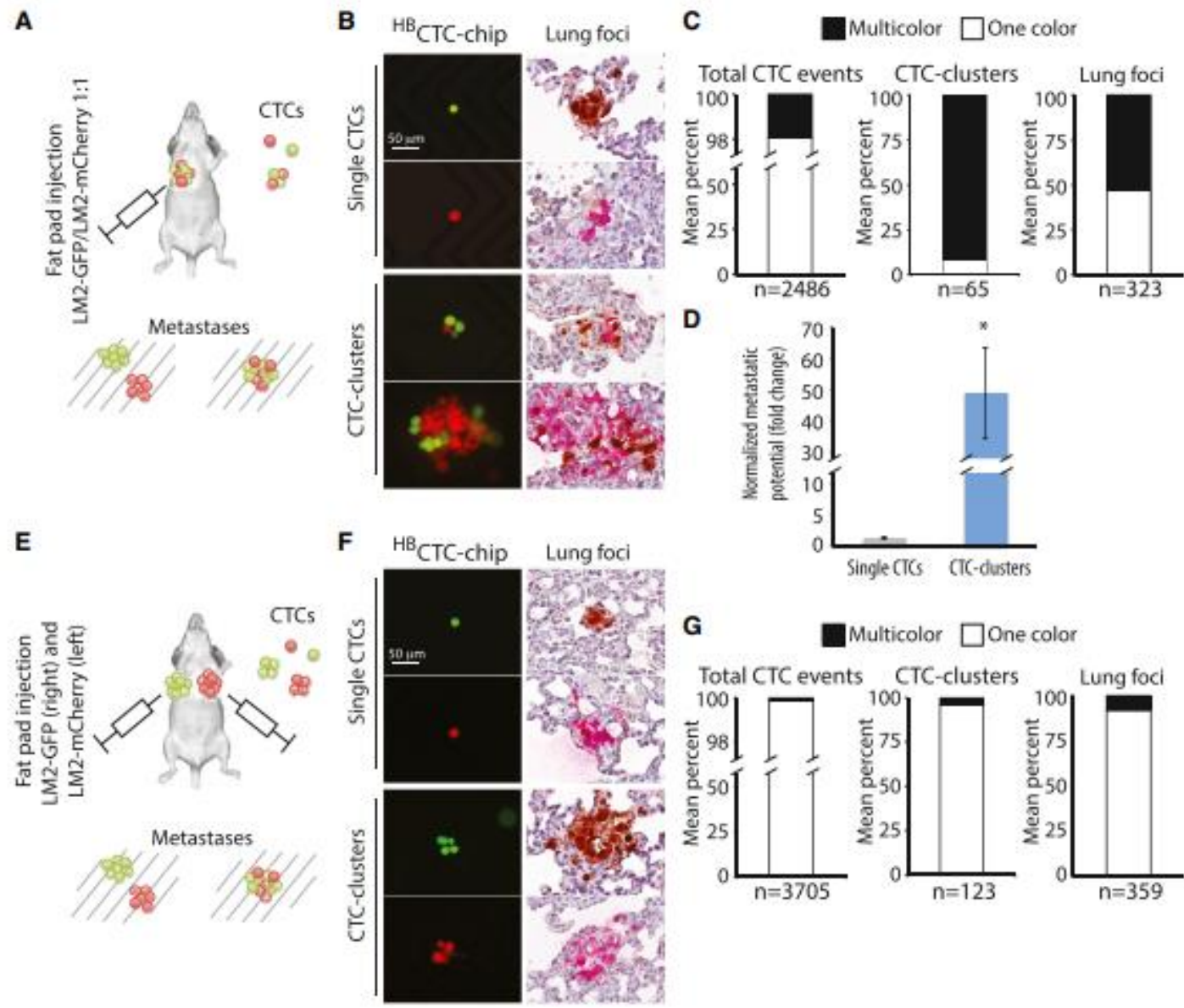 - Cellular Dormancy
  - Tumor Mass Dormancy

A Ring, Front Cell Develop Biol 2022
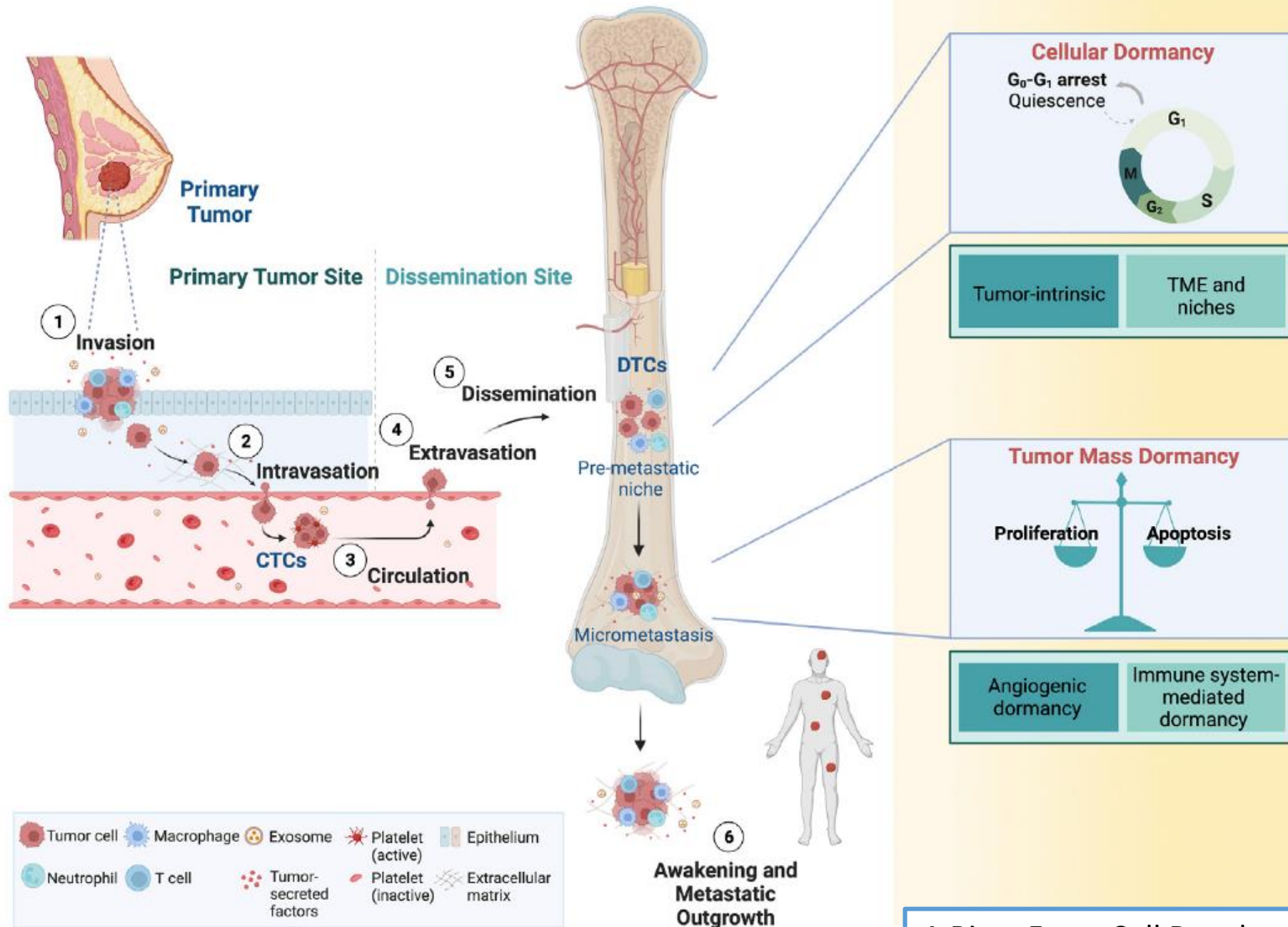
Figure 1. CTC Clusters Demonstrate Increased Metastatic Potential Compared to Single CTCs

N Aceto, Cell 2014
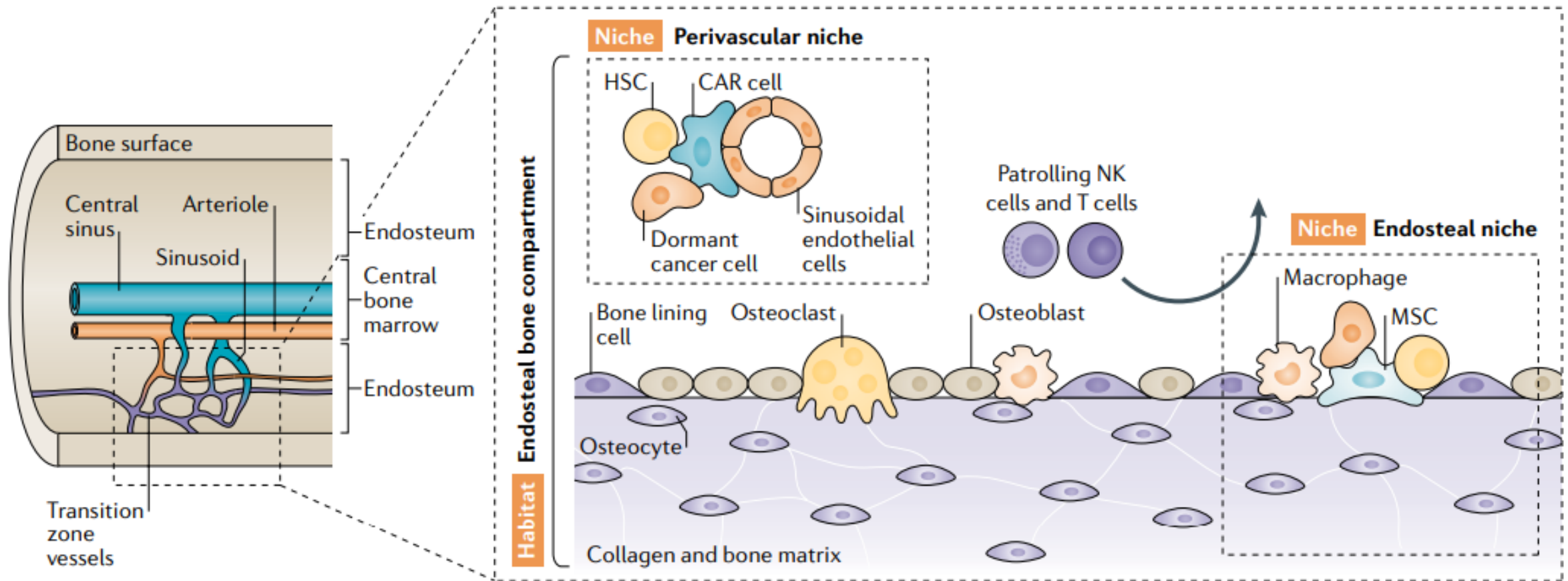
Key Features of of Dormancy
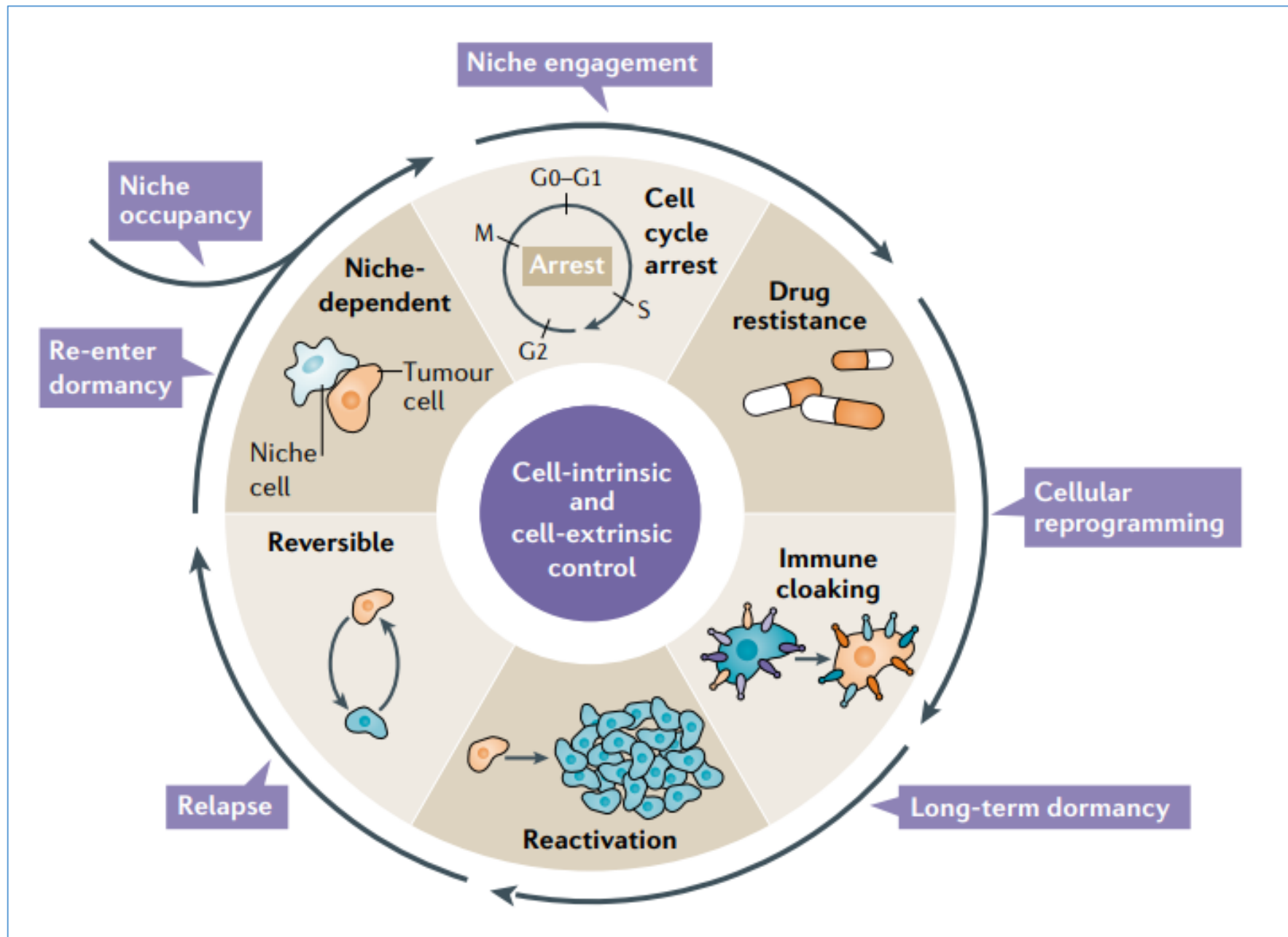
- **Cellular Dormancy**
  - **Cell enter temporary and reversible cell cycle arrest, also known as quiescence**
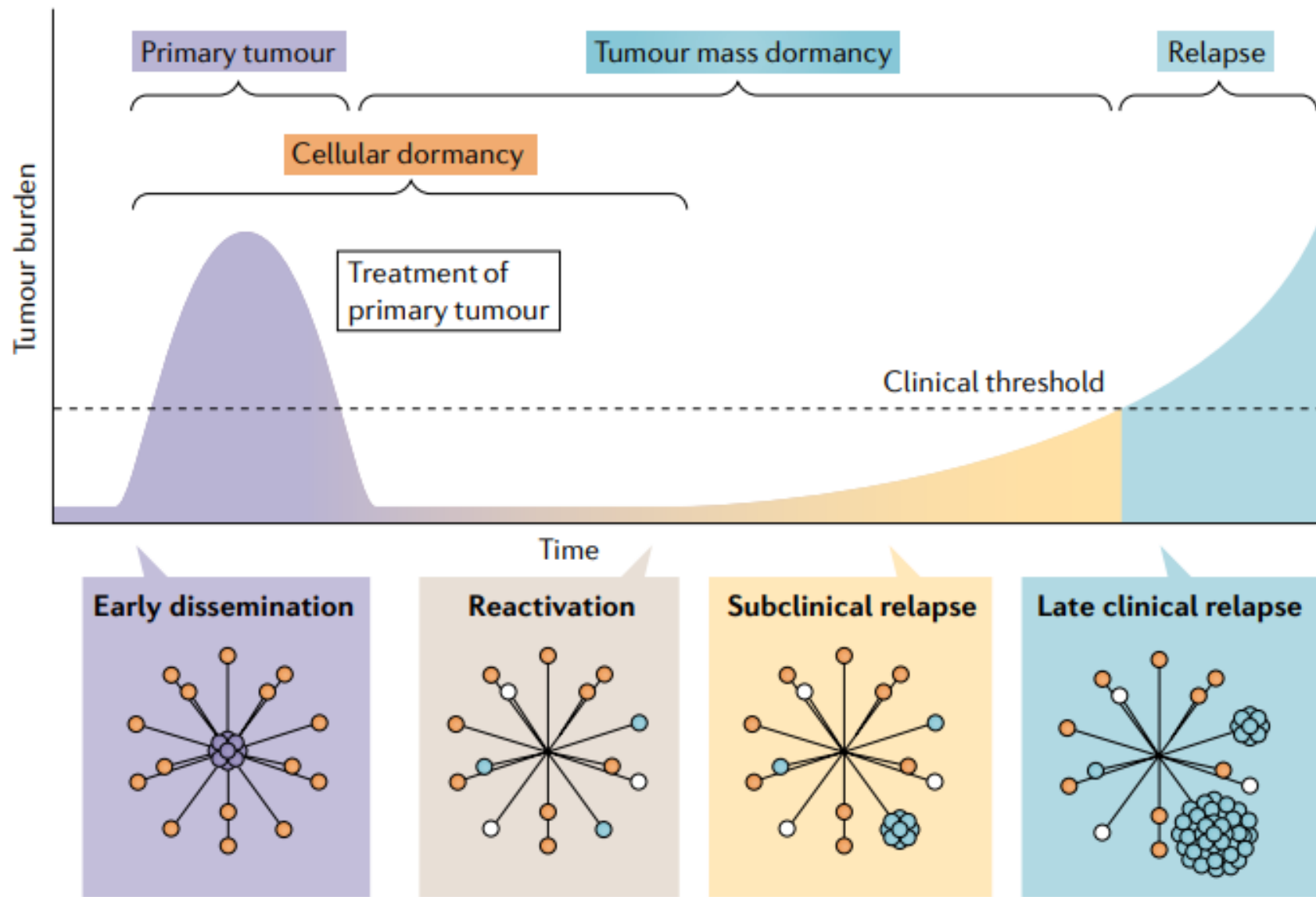
- **Tumor Mass Dormancy**
  - **Cell proliferation and cell death are kept in balance, usually via apoptosis (as a consequence of a lack of angiogenesis or by immune system mediated factors)**
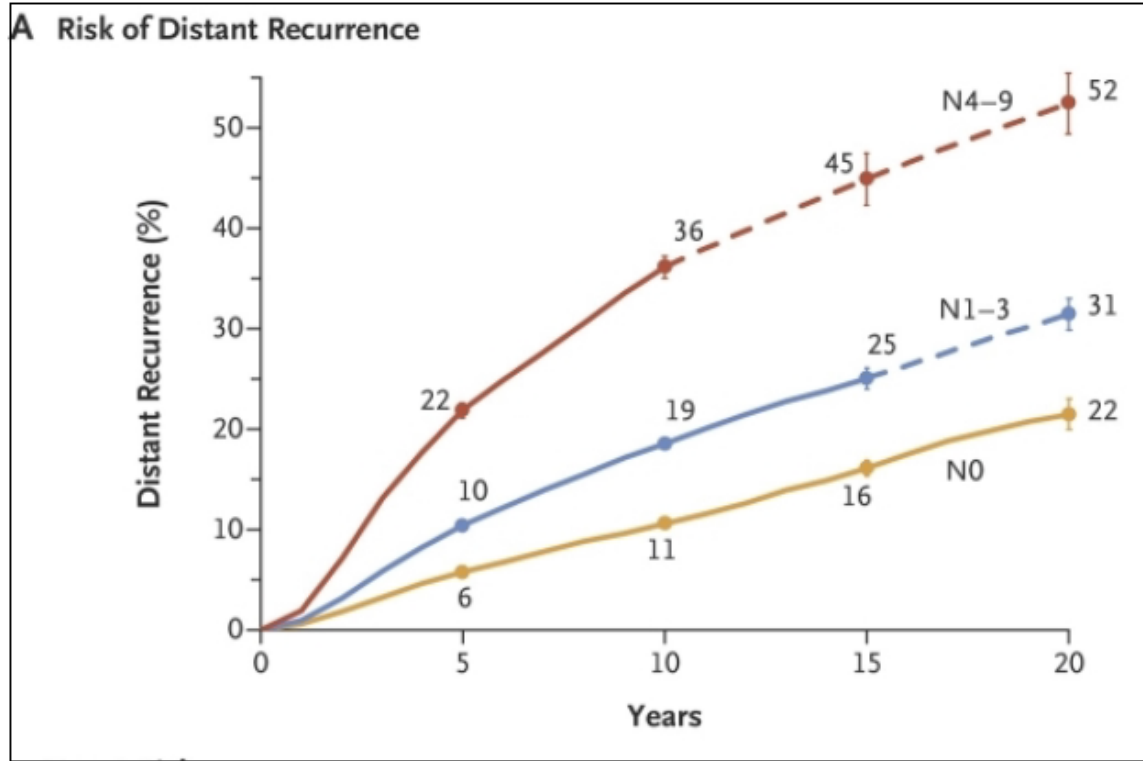
CTCs

- Located in circulation
- Short $T_{1/2}$
- Homo- and heterotypic clusters
- Minimally invasive liquid biopsy

Shared (CTCs ∩ DTCs)

- Small, rare cell population
- Unfavorable prognosis
- Only a small subpopulation is metastatic
- Resistance to anticancer drugs

DTCs

- Different dissemination sites
- Long $T_{1/2}$?
- Cluster composition?
- Invasive BM aspiration

A Ring, Front Cell Develop Biol 2022

Bone surface

Central sinus   Arteriole

Sinusoid

Central bone marrow

Endosteum

Endosteum

Transition zone vessels

Endosteal bone compartment

Niche **Perivascular niche**

HSC   CAR cell

Dormant cancer cell

Sinusoidal endothelial cells

Patrolling NK cells and T cells

Niche **Endosteal niche**

Macrophage

MSC

Bone lining cell   Osteoclast   Osteoblast

Habitat

Osteocyte

Collagen and bone matrix

TG Phan , Nat Rev Cancer 2020

TG Phan , Nat Rev Cancer 2020

Clinical Relevance

TG Phan , Nat Rev Cancer 2020

Late Recurrence: Scope of the Clinical Challenge

A Risk of Distant Recurrence

Pan H et al. *NEJM* 2017

- **>287,000** new breast cancer diagnoses each year in US, **>75% hormone receptor-positive**

- In HR+ breast cancer **>50%** of recurrences occur **more than 5 years** after diagnosis

- Approximately **25%** of patients all with HR+ breast cancer will have a distant recurrence over 20 years
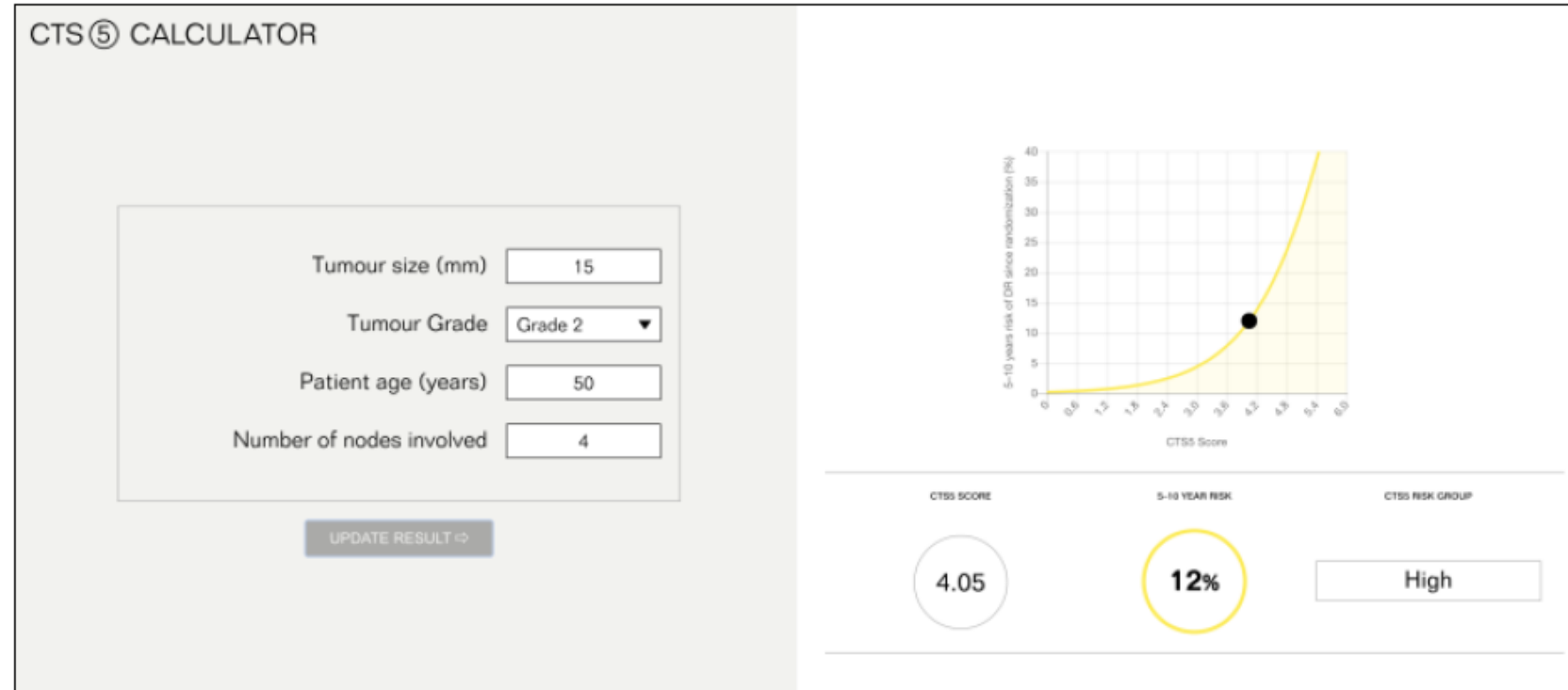
Anatomy-based Tools to Assess Late Risk

- EBCTCG data based on TN stage and grade
  - T1N0 with 5 years of ET:
    - ~13% distant recurrence in years 5-20 if diagnosed before 2000
    - *? ~ 10% distant recurrence in years 5-20 if diagnosed in 2000 or after*

- CTS5: Clinical Treatment Score post-5 years
  - Readily available, inexpensive calculator
  - Utilizes TN stage, grade and age
  - Validated in ATAC and BIG 1-98

ASCO 2022	If a patient is postmenopausal and had invasive breast cancer and is recurrence-free after 5 years of adjuvant endocrine therapy, the <u>CTS5 web tool may be used to calculate the estimated risk of late recurrence (recurrence between years 5-10) that could assist in decisions about extended endocrine therapy</u> (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate)

Pan H et al. *NEJM* 2017; Pan H et al, SABCS (GS2-04), 2019 Dowsett, M et al., *JCO* 2018; Andre, F et al, *JCO* 2022

CTS5 Calculator

- Readout 5-10-year risk of distant recurrence
  - Low: <5%
  - Intermediate: 5-10%
  - High: > 10%

- Limited validity in premenopausal women

- Limited data in HER2+ disease

- Overestimates risk in those who have received extended endocrine therapy

Website: https://cts5-calculator.com/

Dowsett, M et al, *JCO* 2018; Noorhoeck, I et al, *JCO* 2020; Richman, J et al, *BCRT* 2021; Sestak, I et al SABCS 2019; Tajiri W et al, *Breast Cancer* 2021; Pai T et al, ASCO 2022

Genomic Assays to Assess Late Risk

Breast Cancer Index (BCI)

- Commercially available

- Combines the 2-gene HOXB13:IL17BR ratio with the molecular grade index from 5 proliferation genes in a linear model

- Reports recurrence risk in years 5-10 and benefit to extended anti-estrogen therapy

- Absolute reduction of recurrence risk 3.8% (NSABP B-42) to 16.5% (MA-17)

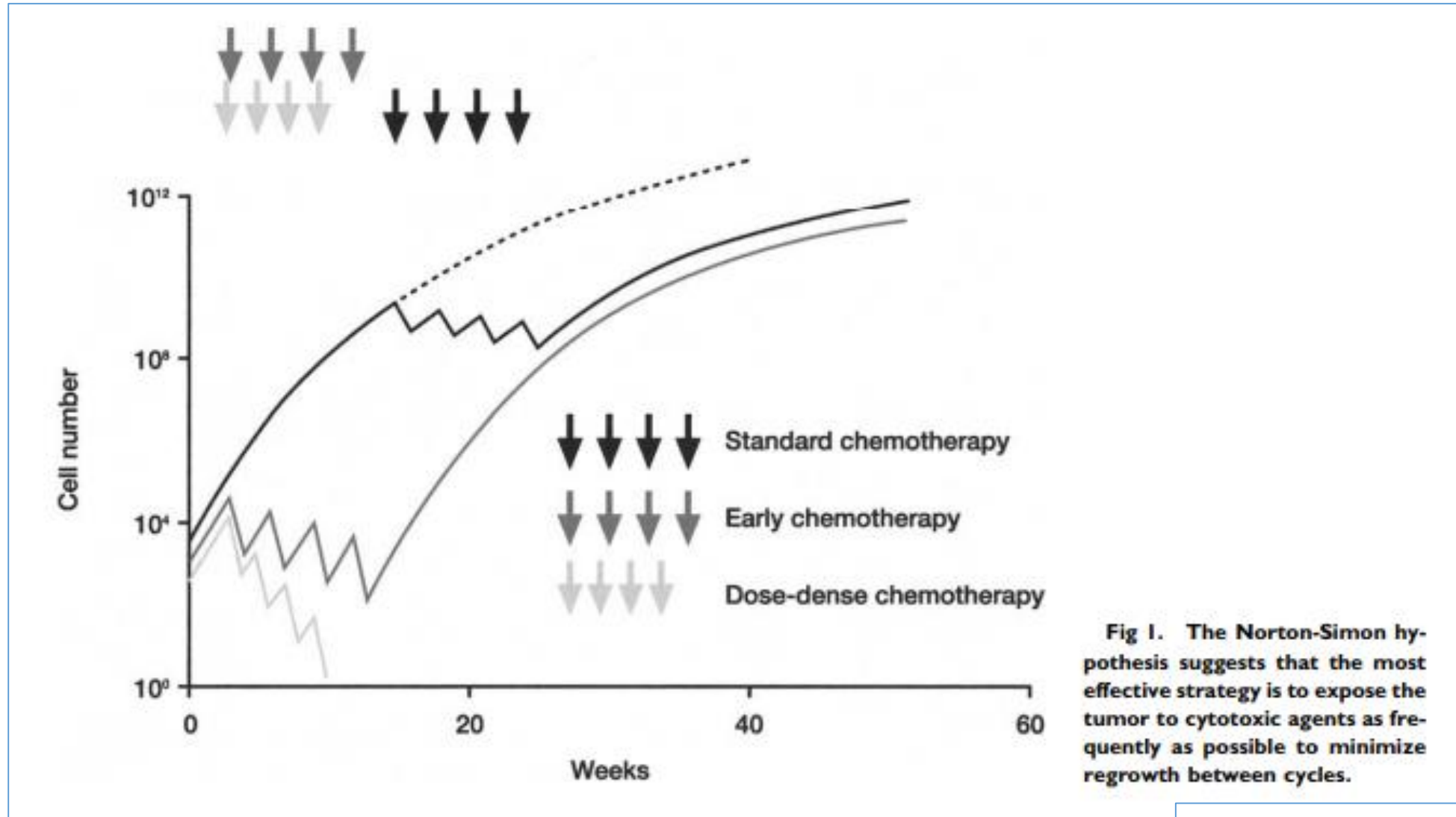|	
ASCO 2022	*In N0-N1 breast cancer treated with 5 years of endocrine therapy without recurrence, the clinician <u>may offer BCI test to guide decisions on extended endocrine therapy</u>* (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate)
NCCN 2021	*Prognostic, as well as predictive of benefit of extended adjuvant endocrine therapy* (Predictive benefit seen in secondary analyses of MA-17, Trans-aTTom, and IDEAL trials) (NCCN Category of Evidence and Consensus: 2A)

- Some genomic assays may identify patients at low risk of recurrence, who may be candidates for de-escalation
- Prosigna (ROR) utilized in the LA LEAST Trial: Limited Adjuvant Endocrine Therapy for Low Risk Breast Cancer

Zhang, Y et al, *Clin Cancer Res*, 2017; Sgroi, DC et al *JNCI*, 2013; Mamounas, T et al ASCO 2021; Andre, F et al, *JCO* 2022; Sestak I et al. *JAMA Onc*, 2018

Research & Trials

Shortcomings to achieve cure

- **Clonal composition and biology of disseminated cells and micrometastases differs from larger tumor lesions**

- **DTC enter a state of dormancy protecting them from detection and eradication**

- **Current diagnostic tools and systemic therapies are not designed to detect and target dormant cells**

Mathematical Modelling

Fig 1. The Norton-Simon hypothesis suggests that the most effective strategy is to expose the tumor to cytotoxic agents as frequently as possible to minimize regrowth between cycles.

Adjuvant CT Evolution

- CMF
- AC
- FAC
- A → T
- dd A → T

Some paradoxical effects of CT

- **Promoting Metastases**
  - **Enhancing Vascular Permeability**
  - **Activation of Inflammatory Pathways**

- **Promoting Tumor Dormancy**

- **Promoting premetastatic niches**

- **Promoting epithelial-mesenchymal plasticity**

T-DM1 Performance

		ORR (%)	PFS (mos)	Ref
Metastatic	TH3RESA	**31**	**6**	IE Krop, Lancet Oncol 2014
	EMILIA	**44**	**9**	S Verma, NEJM 2012
	MARIANNE	**59**	**14**	E Perez, JCO 2017
Non-Metastatic	KATHERINE	**Eradication/Cure**		G von Minckwitz, NEJM 2019

The Old Paradigm Resists

- **Not only for CT & HT**

- **But even for**
  - **Anti-HER2 Agents**
  - **Abemaciclib**
  - **Olaparib**
  - **(ICI)**

Blood-Based Biomarkers for Minimal/Measurable Residual Disease (MRD)

- **Accumulating data for prognostic implications of blood-based biomarker detection in early-stage BC (e.g. ctDNA)**

  - MRD detection is associated with **_extreme risk_** of recurrence in subsequent 1-3 years

  - How these will be used still undergoing validation

  - Ease of use is promising

  - Could dramatically alter how we counsel patients

Parsons et al. *CCR* 2020
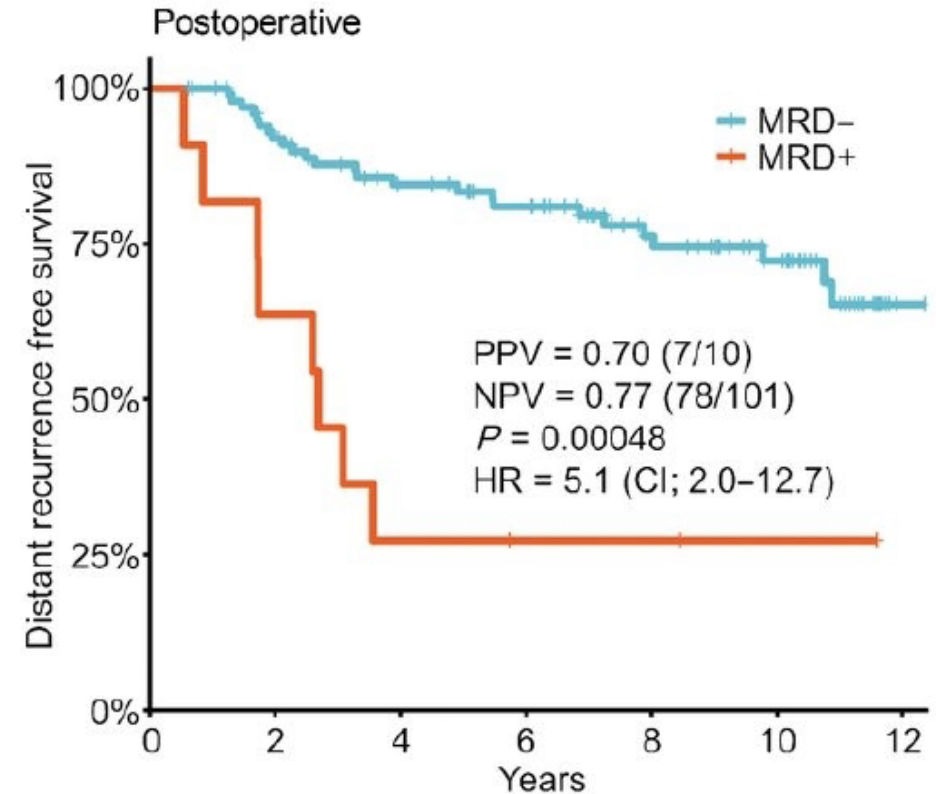
ctDNA to Predict Late Recurrence

Lipsyc-Sharf M, et al *JCO* 2022
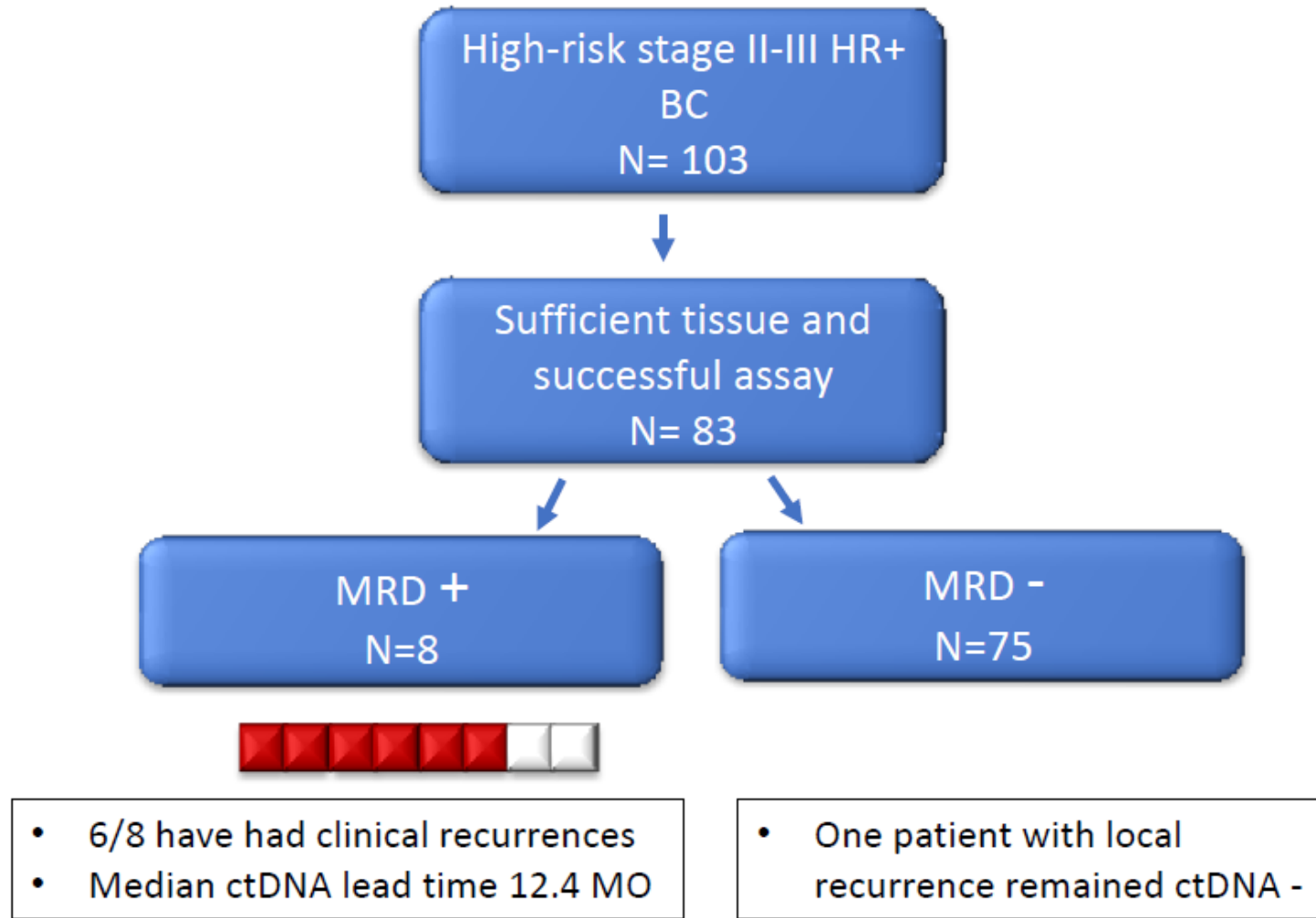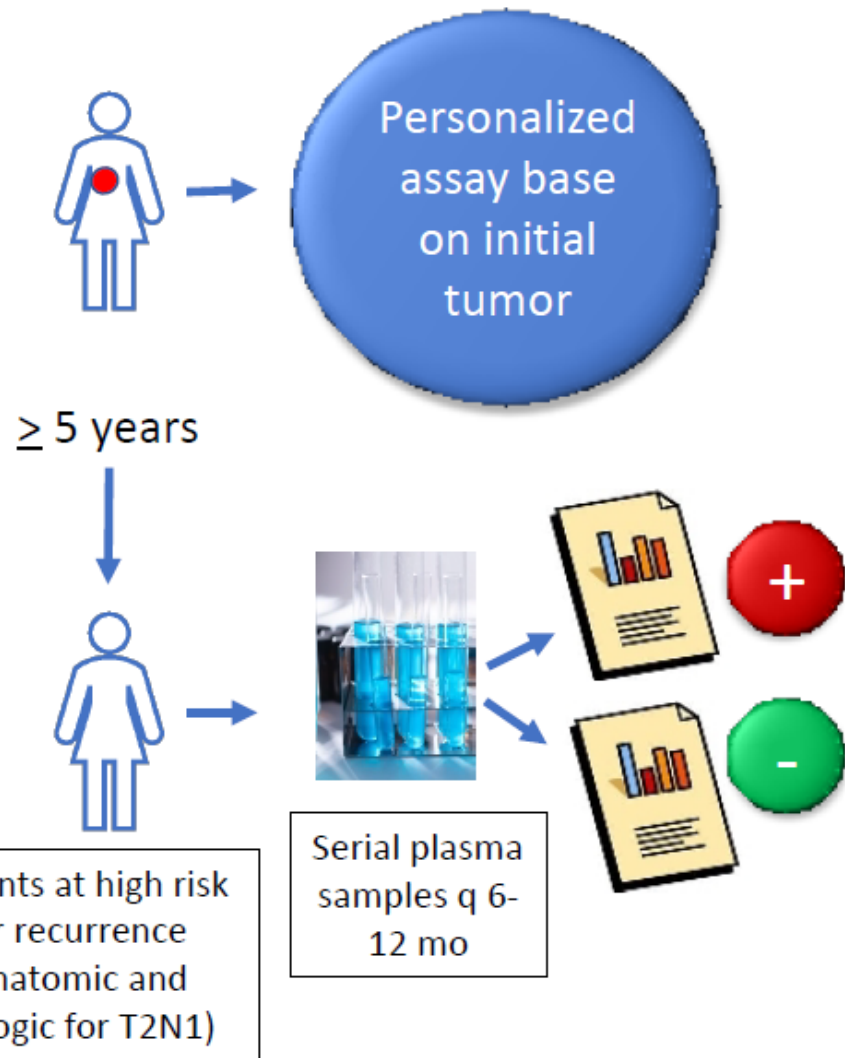
Challenges to Targeting Bone Marrow DTCs
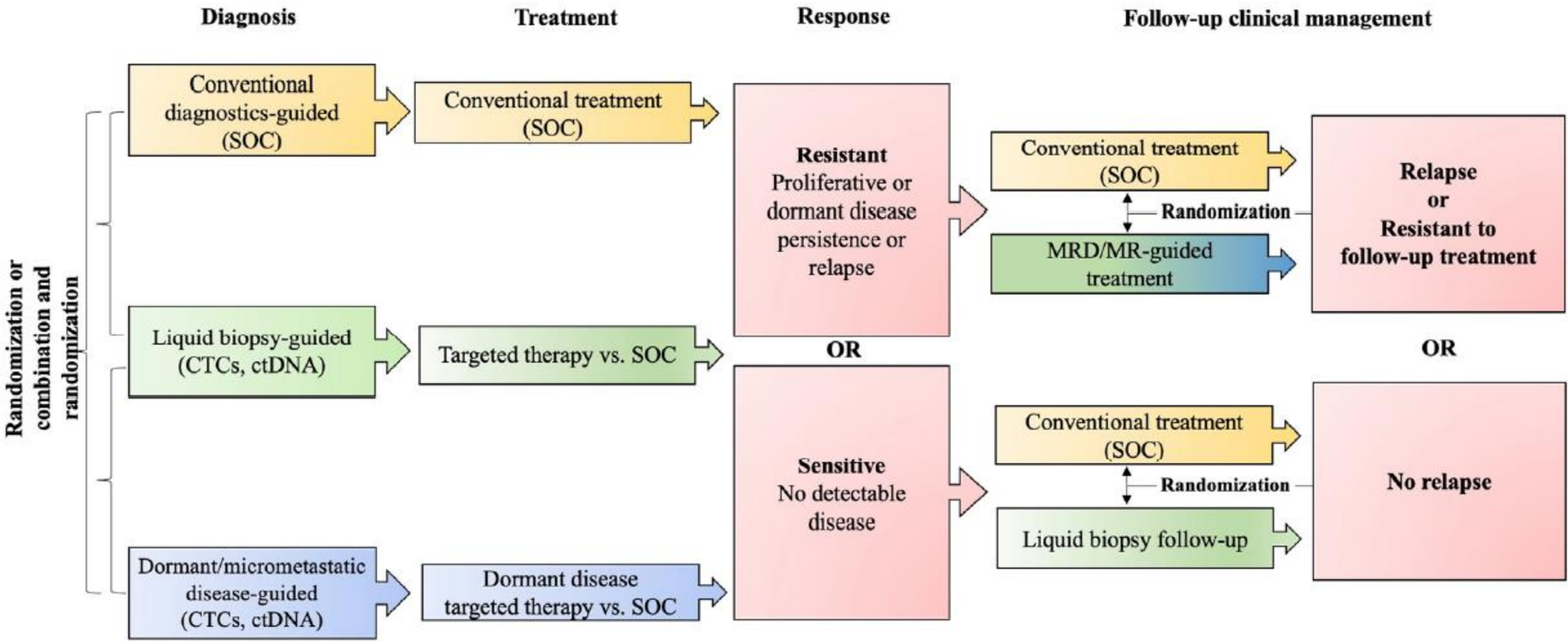
Systemic recurrence-free survival
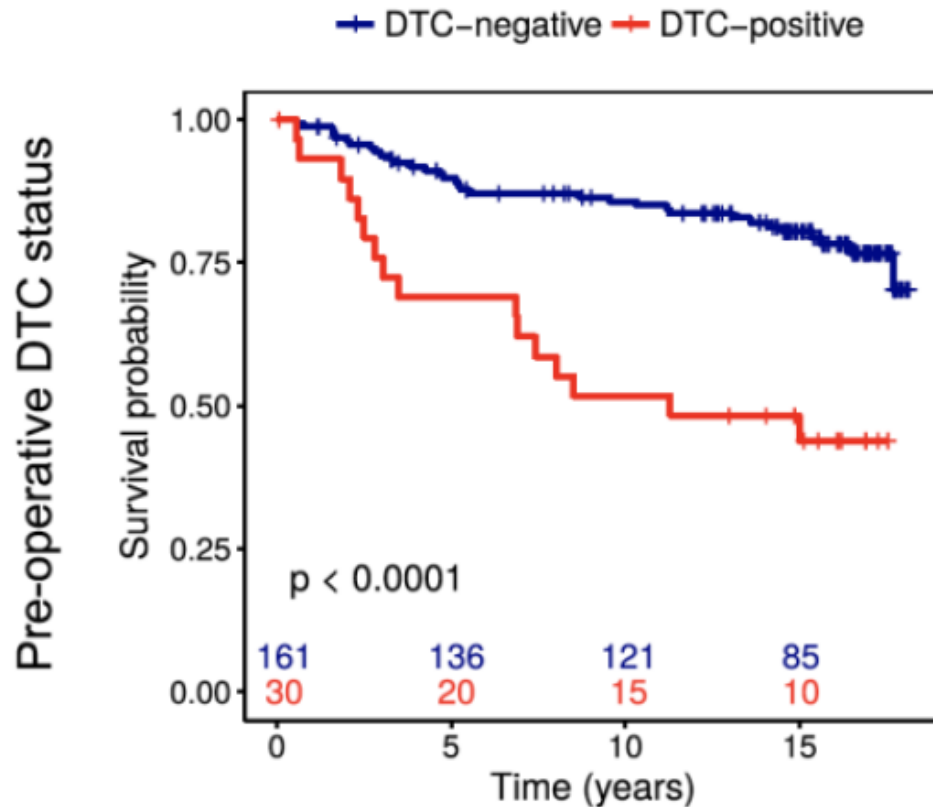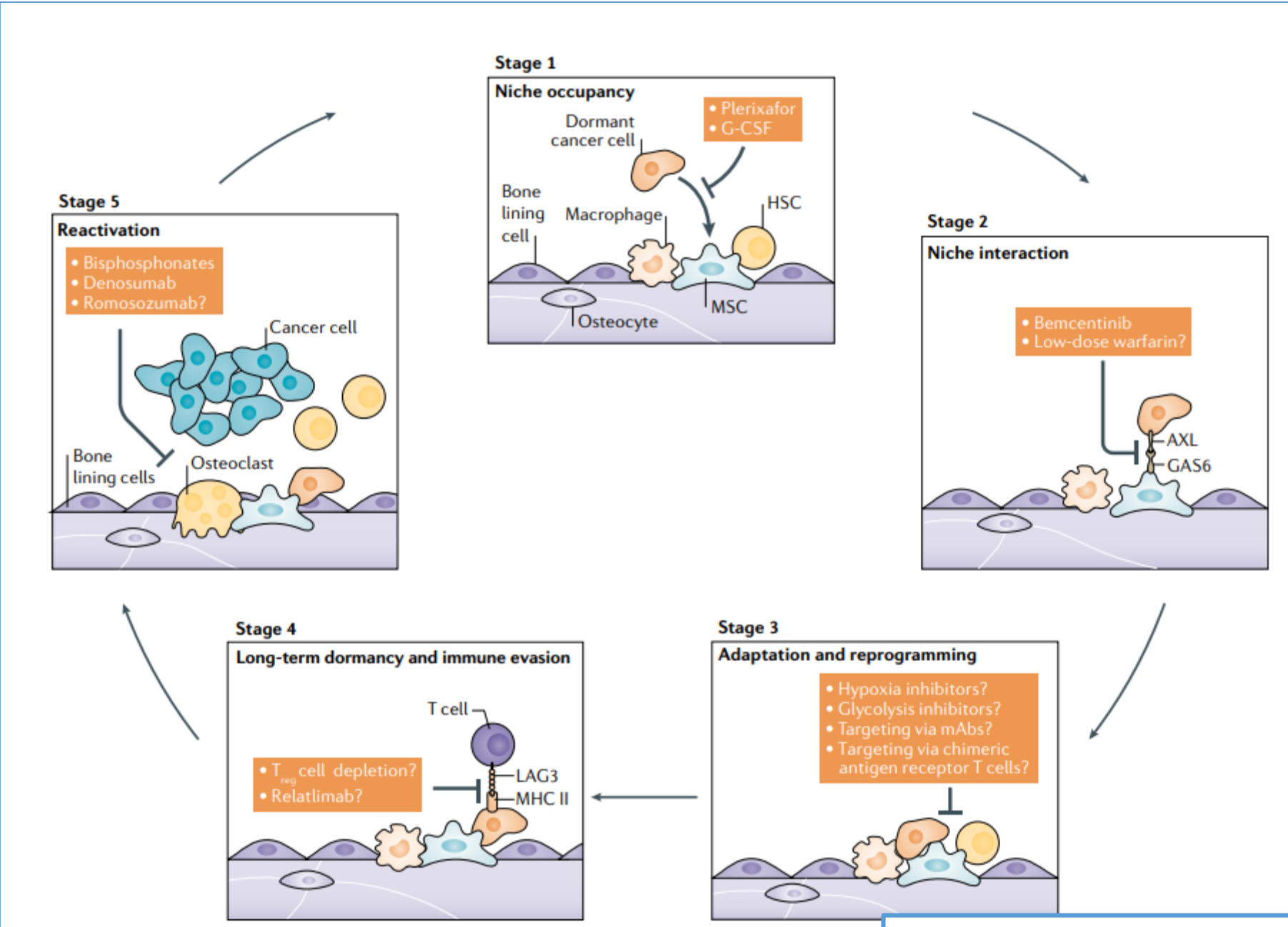

Tjensvoll K et al. *BMC Cancer*, 2019

Disseminated Tumor Cells (DTCs) in Bone Marrow:

Imperfect Biomarker

- Many do not have systemic recurrence

- Many recur who were initially negative

- Difficult to access, especially repeatedly

- Sampling issues

A Ring, Front Cell Develop Biol 2022

TG Phan , Nat Rev Cancer 2020

Comprehensive Cancer Centers

Care (not only antitumor drugs)

DMT (+ newer boards)
Geriatric Assessment
Clinical Pharmacy
Remote Surveillance
Cardio-Oncology
Early & Simultaneous Palliative Care
Support
Nutrition
Psycho-Oncology
Oncology Nursing
Gender Medicine
Cancer Survivorship Plans

Research

Circular Drug Development
Newer Phase I
Biomarkers
RWD & RWE

Education

Professionals
Managers
Patients