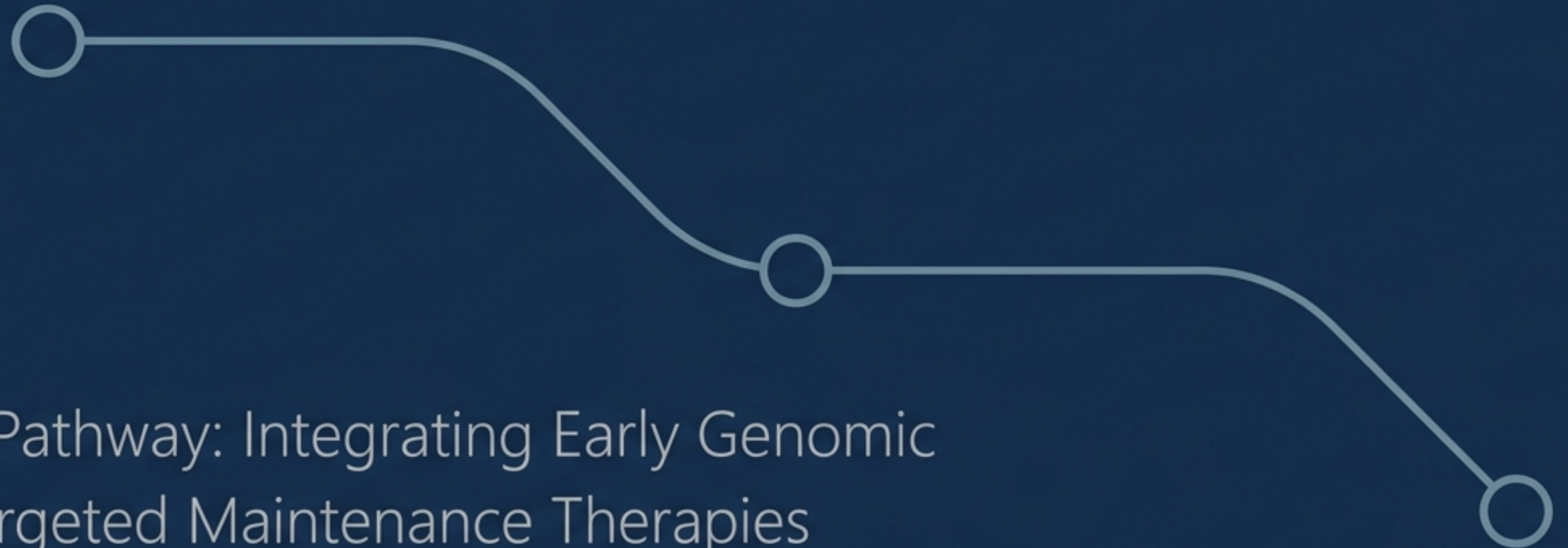
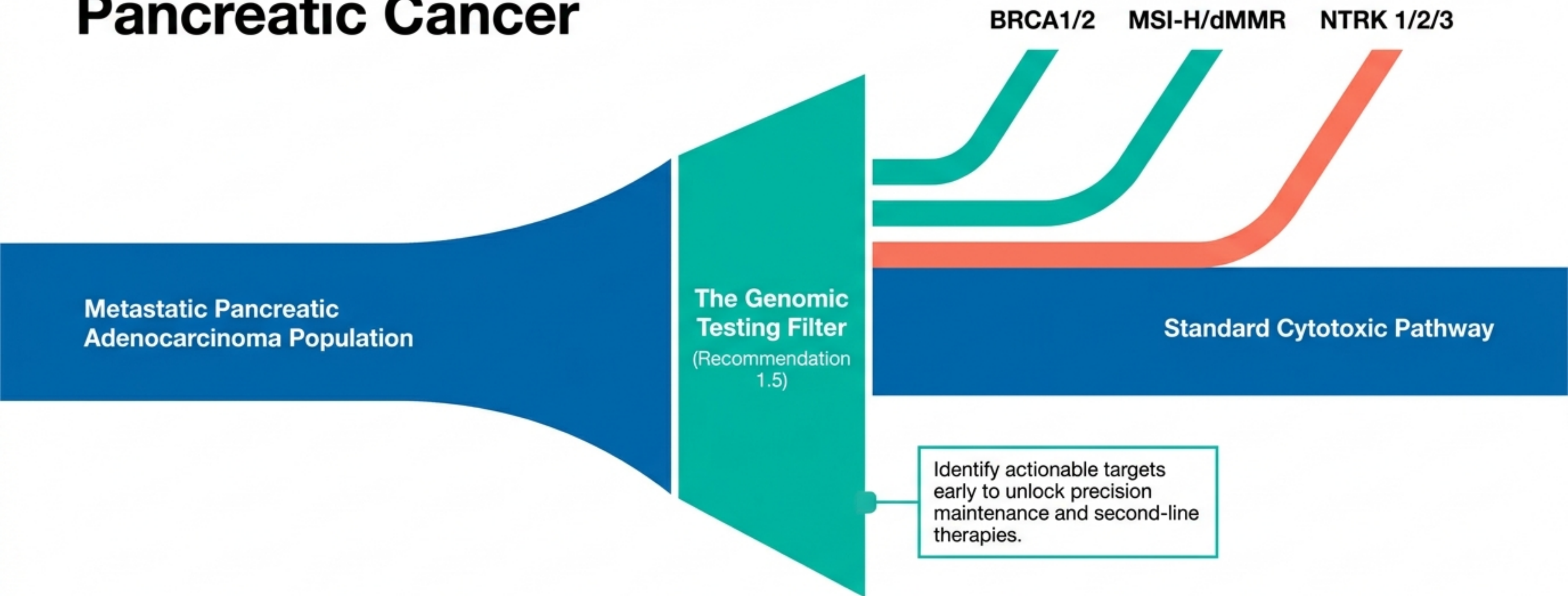


Metastatic Pancreatic Cancer

ASCO Clinical Practice Guideline Update (2020)



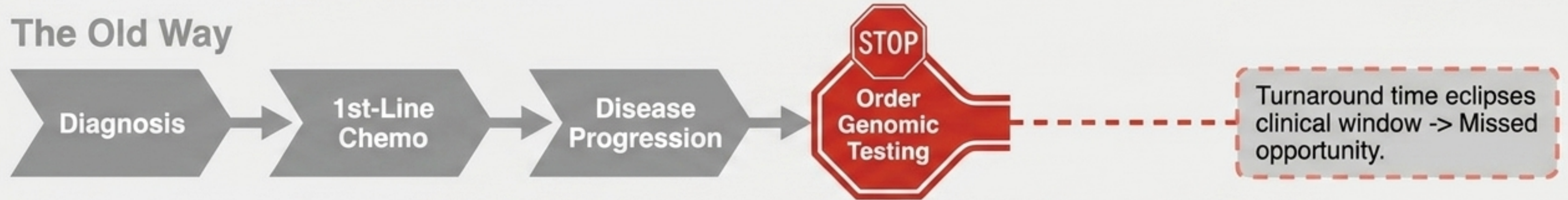
The Shifting Paradigm in Pancreatic Cancer



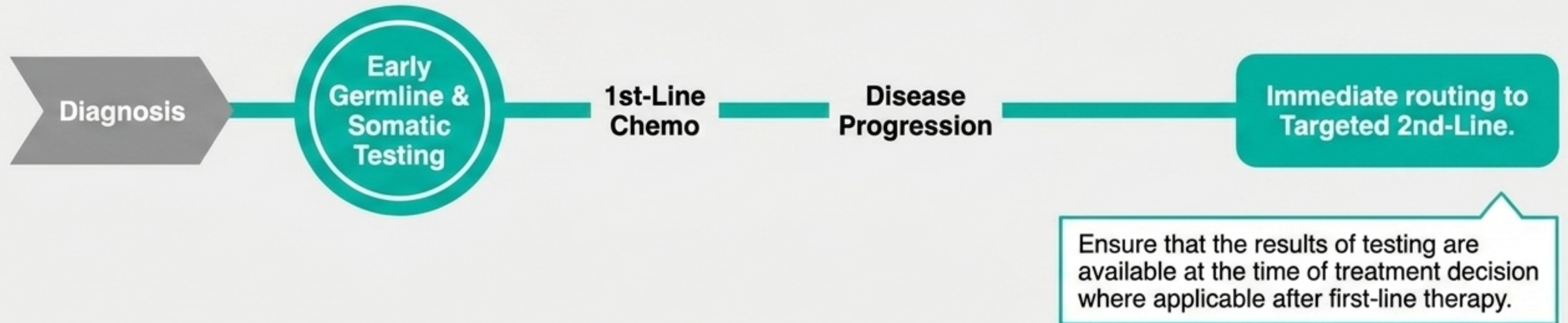
The Urgency of Early Genomic Assessment

Recommendation 1.5 mandates early testing for actionable genomic alterations.

The Old Way



The Precision Pathway



The Biomarker Blueprint



Germline/Tumor
BRCA1 or BRCA2



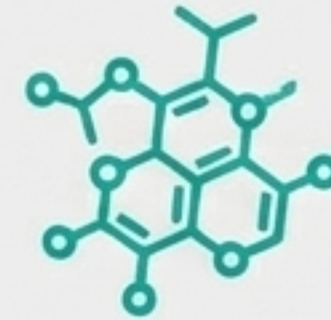
PARP Inhibitor
(Olaparib)



NTRK 1/2/3
Gene Fusions



TRK Fusion Inhibitors
(Larotrectinib or Entrectinib)



MSI-H or dMMR



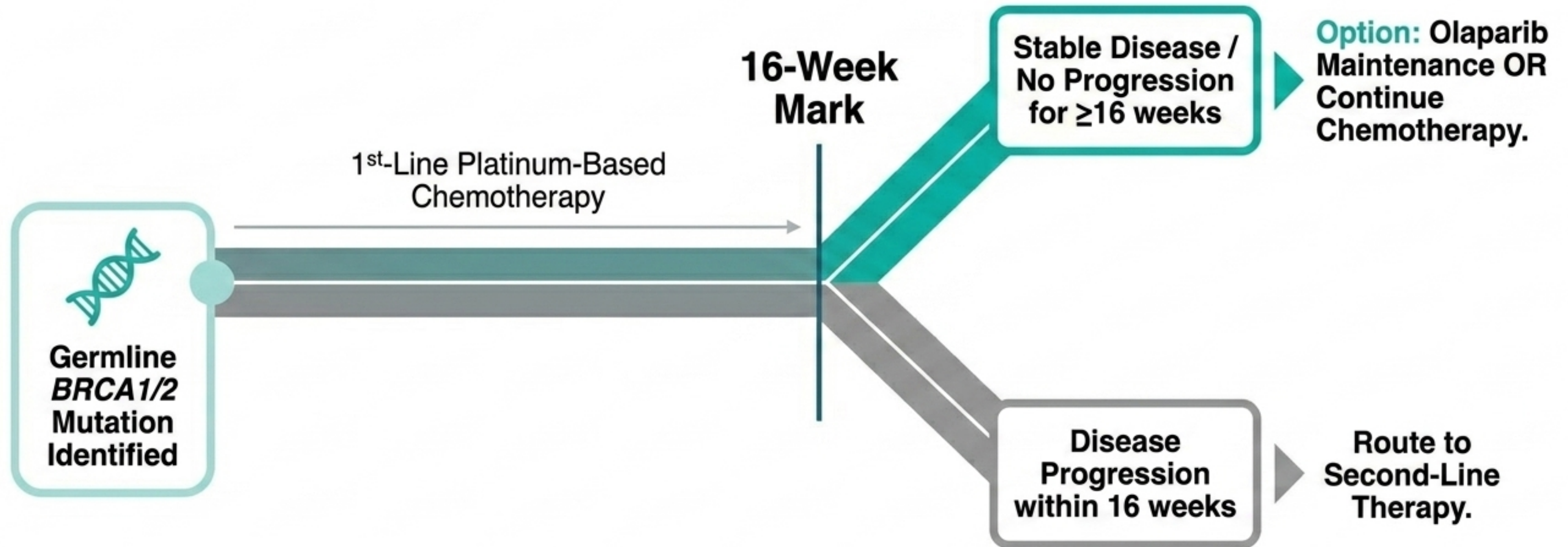
PD-1 Inhibitor
(Pembrolizumab)

Exclude variants of unknown significance for BRCA. Include genetic counseling for germline testing.

Systemic Foundations: First-Line Cytotoxic Routing

Clinical Profile	Recommended Regimen
ECOG PS 0-1 + Favorable Comorbidities + Access to port/pump	FOLFIRINOX (Strong Recommendation)
ECOG PS 0-1 + Relatively Favorable Comorbidities	Gemcitabine + nab-paclitaxel (Strong Recommendation)
ECOG PS 2 OR Precluding Comorbidities	Gemcitabine alone (Addition of nab-paclitaxel, capecitabine, or erlotinib optional with dose adjustments) (Moderate Recommendation)
ECOG PS 3 or poorly controlled conditions	Case-by-case / Optimize supportive care

The Platinum Runway: Routing to Olaparib Maintenance



Shared Decision Making parameters: Maximum response achieved, cumulative toxicities, patient preference, cost.

PARP Inhibition: The POLO Trial Data

Maintenance Olaparib vs. Placebo in Germline BRCA-Mutated Metastatic Pancreatic Cancer

Efficacy

HR 0.53

Progression-Free Survival

(95% CI, 0.35 to 0.82) | Moderate certainty,
large magnitude of effect.

Overall Survival Hazard Ratio 0.91 (No significant OS difference at interim analysis).

Toxicity Profile

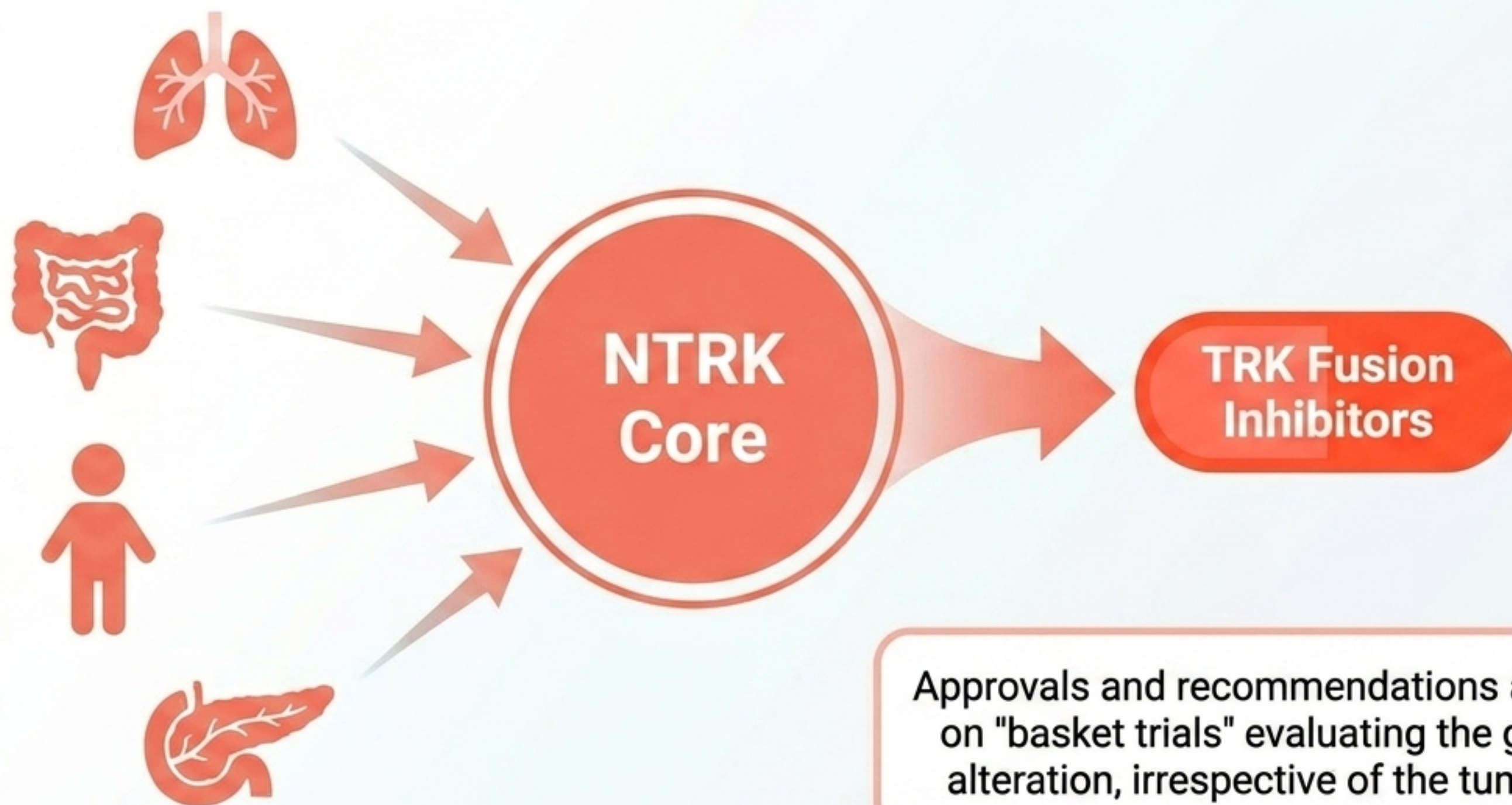


Increased risk of discontinuation due to adverse events

(Relative Risk 3.3)

The Tissue-Agnostic Paradigm

NTRK fusions are rare in pancreatic cancer (~0.34%), but drive profound responses regardless of tumor origin.



TRK Inhibition: Larotrectinib Efficacy

Phase I/II Basket Trial Data in NTRK Fusion-Positive Cancers.

Efficacy



Overall Response Rate

(13% Complete, 62% Partial)

55% Progression-free at 1 year.

Toxicity Profile

- ⚠️ 93% Grade 1/2 Adverse Events.
- ⚠️ Most common Grade 3/4:
 - Anemia (11%)
 - Increased ALT/AST (7%)
 - Decreased neutrophils (7%)

TRK Inhibition: Entrectinib Efficacy

Integrated Analysis of Three Phase I-II Trials (STARTRK-1, STARTRK-2, ALKA-372-001)



Objective Response Rate

(7% Complete, 50% Partial)

Median Duration of Response: 10.4 months. | Median PFS: 11.2 months.

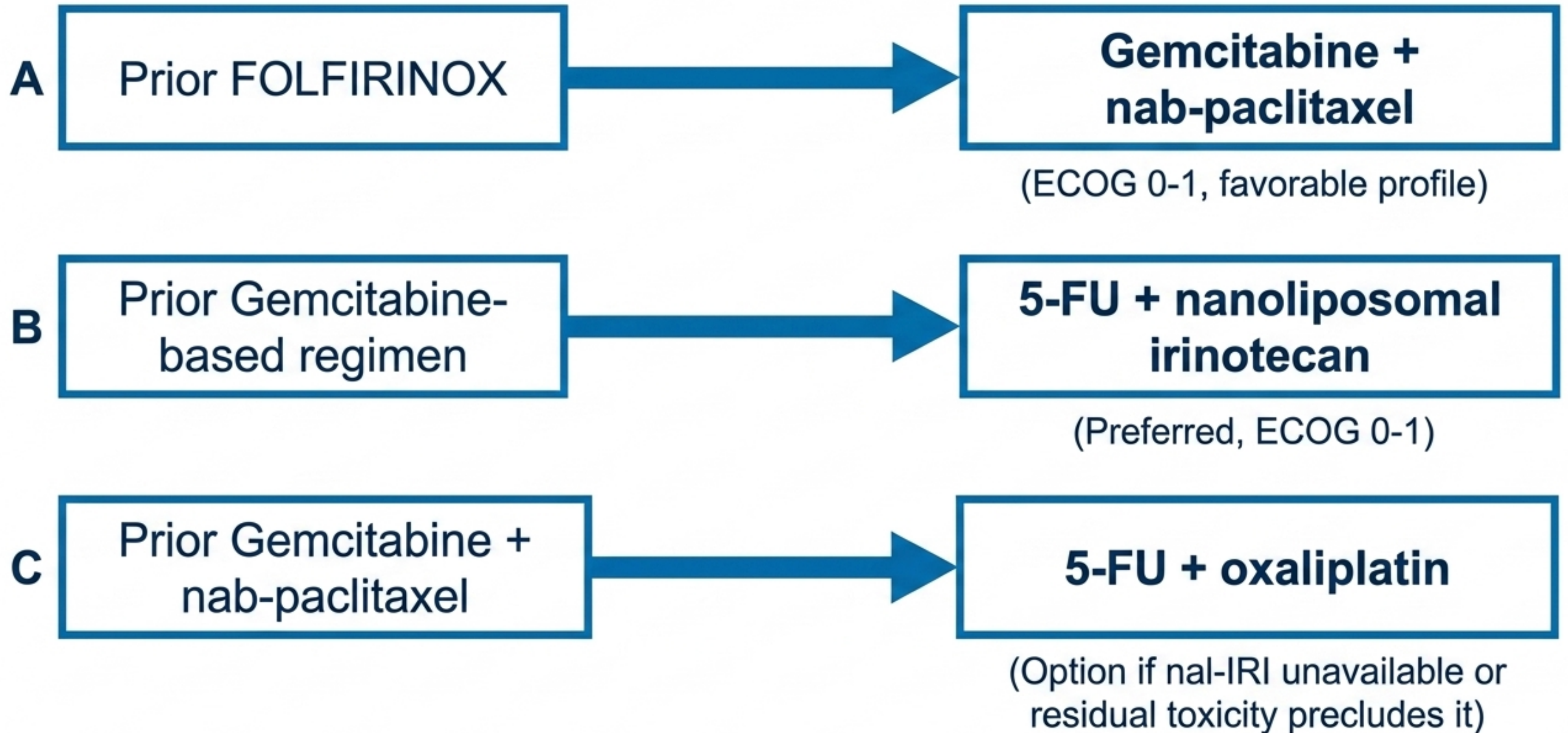
Toxicity Profile

- ⚠ Most common Grade 3/4 Adverse Events:
- ⚠ - Anemia (12%)
- ⚠ - Increased weight (10%)
- ⚠ - Fatigue (7%)

The Precision Portfolio: Targeted Second-Line Options

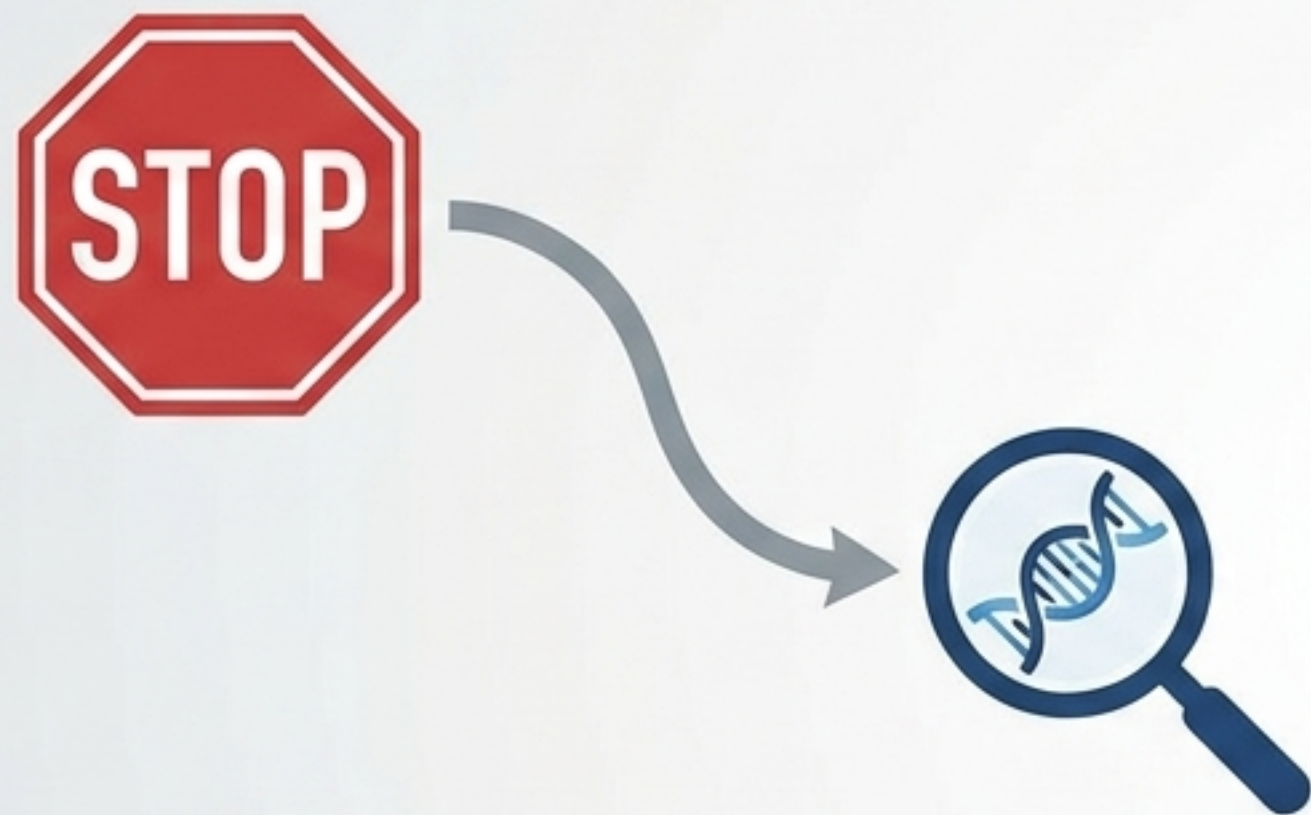
Olaparib	Pembrolizumab	Larotrectinib	Entrectinib
Target: Germline BRCA1/2 ✓	Target: MSI-H or dMMR ✓	Target: NTRK Fusions ✓	Target: NTRK Fusions ✓
Setting: Maintenance (post-16 wks platinum) ✓	Setting: Second-line ✓	Setting: Second-line ✓	Setting: Second-line ✓
Key Metric: PFS Benefit ✓	Key Metric: Endorsed from 2018	Key Metric: 75% ORR ✓	Key Metric: 57% ORR ✓
Rec Strength: Moderate ✓	Rec Strength: Strong ✓	Rec Strength: Moderate ✓	Rec Strength: Moderate ✓

Cytotoxic Routing: Non-Targeted Progression



Third-Line Therapy & Ongoing Surveillance

Third-Line Stance



Third-Line Stance (Rec 3.8): No data available to recommend 3rd-line or greater cytotoxic therapy.

Clinical trial participation is strongly encouraged.

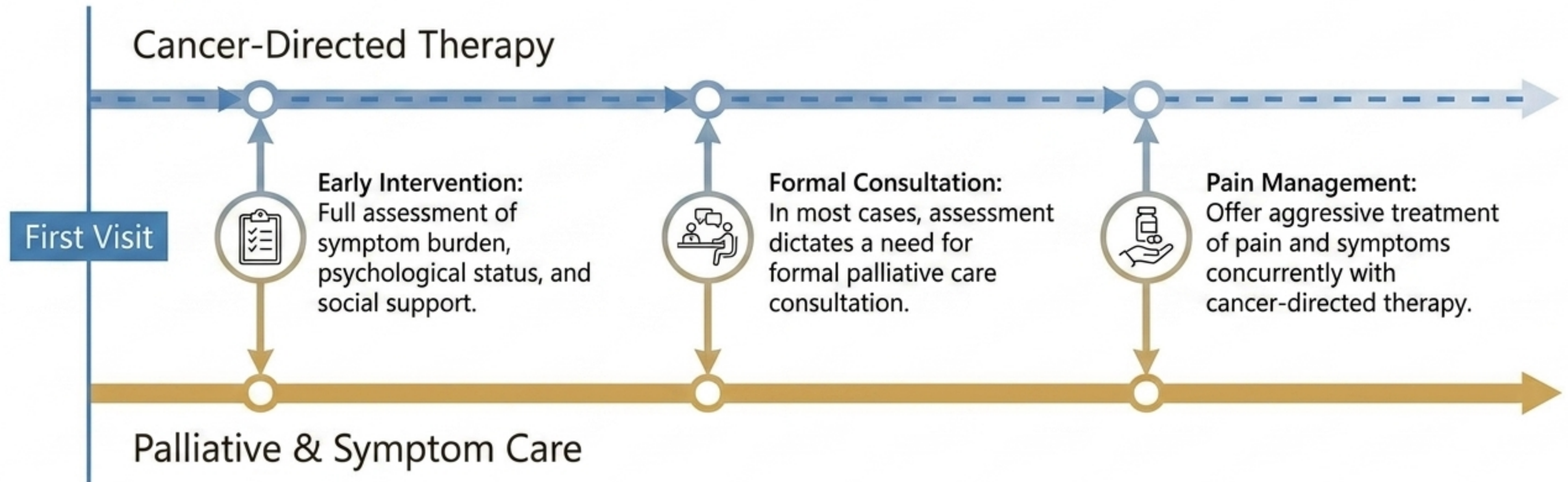
Imaging Loop



Imaging Loop (Rec 6.1): CT scans with contrast every 2 to 3 months.

Exclusions: Routine use of PET scans is NOT recommended. CA19-9 is NOT an optimal substitute for imaging.

The Parallel Pathway: Integrated Palliative Care



The Complete Precision Pathway

2020 ASCO Metastatic Pancreatic Cancer Treatment Algorithm

