MOLECULAR SEQUENCING AND NOVEL THERAPEUTICS IN PANCREATIC CANCER

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PANCREATIC CANCER PROGRAM: MED ONCOLOGY LEAD

SOLID TUMOR CELL THERAPY: GI ONCOLOGY LEAD

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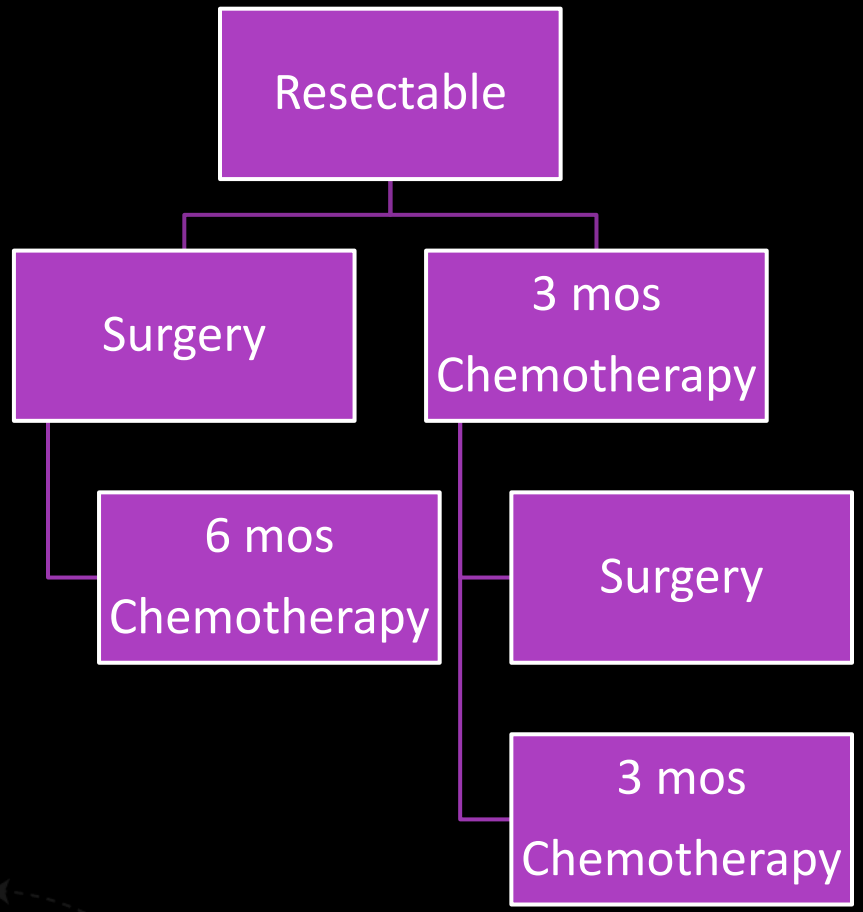
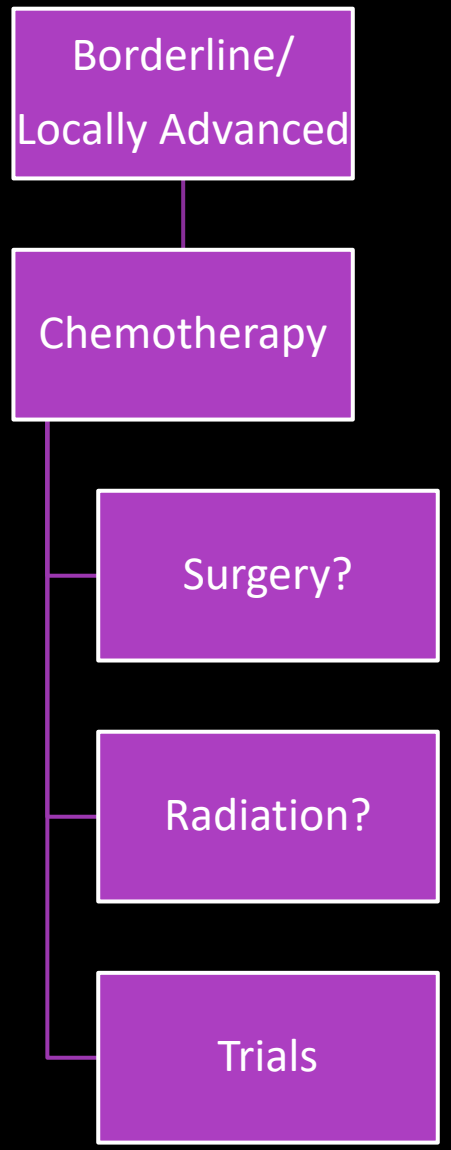
LEARNING OBJECTIVES

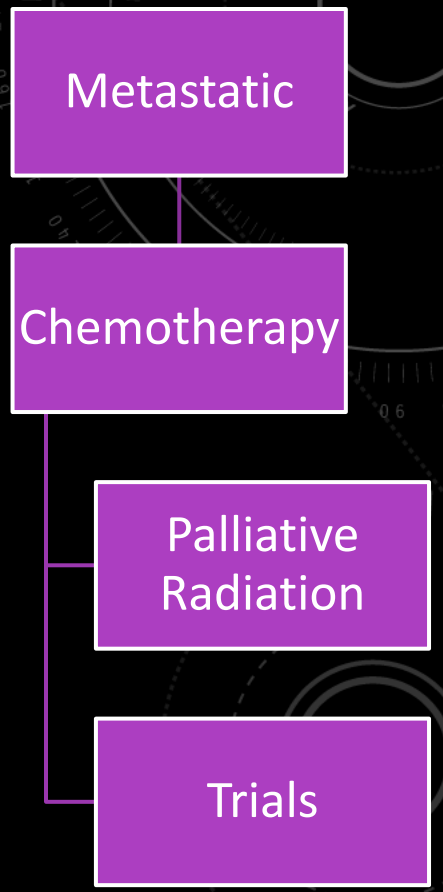
- When and How to Order Molecular and Genomic Tests
- Interpreting the Molecular and Genomic Information
- Applying the Molecular and Genomic Information to Practice/Trials
- Integrating ctDNA into Practice

PANCREATIC CANCER CARE 2024

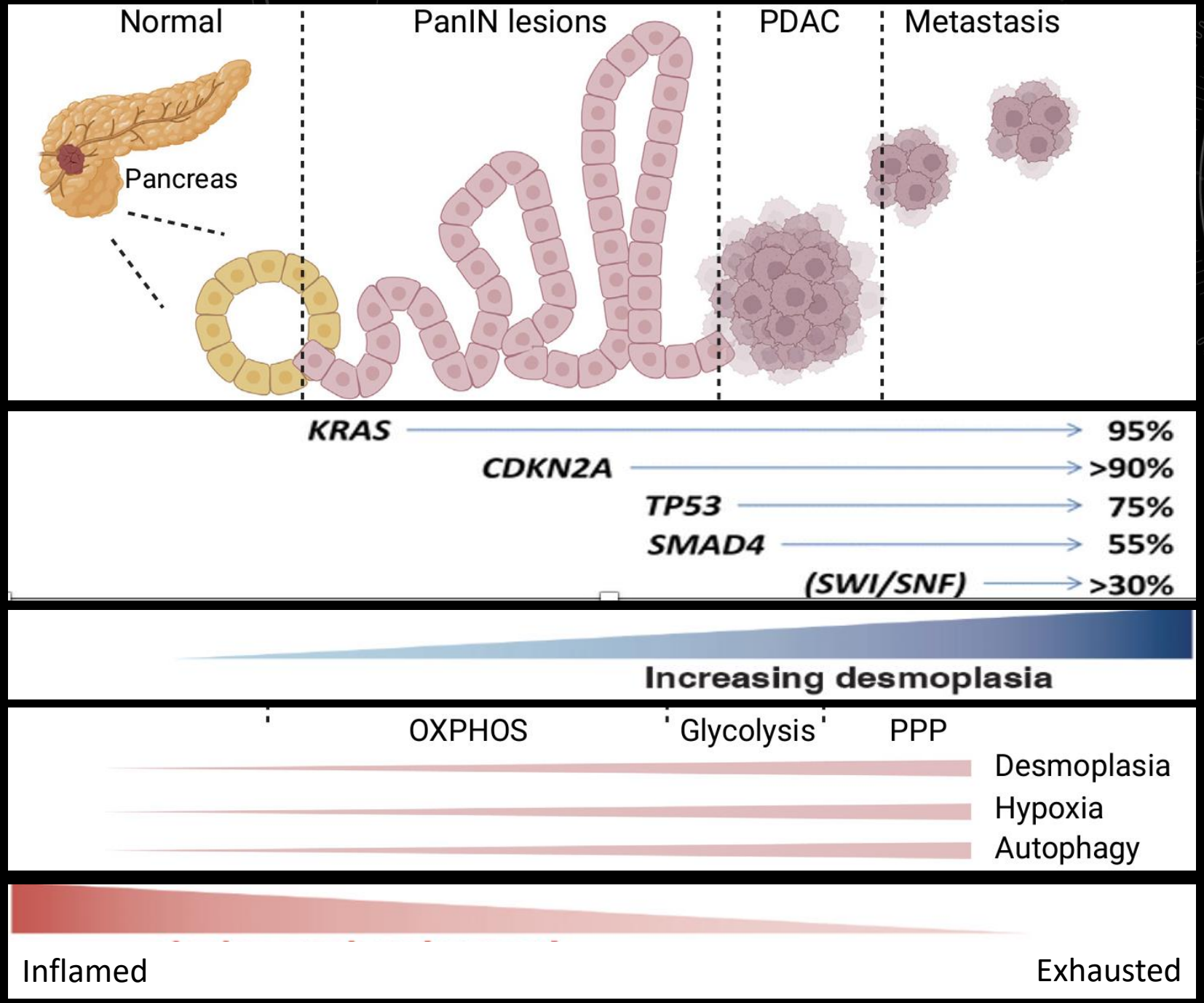


Only Potentially Curable Pathway





Not Curable



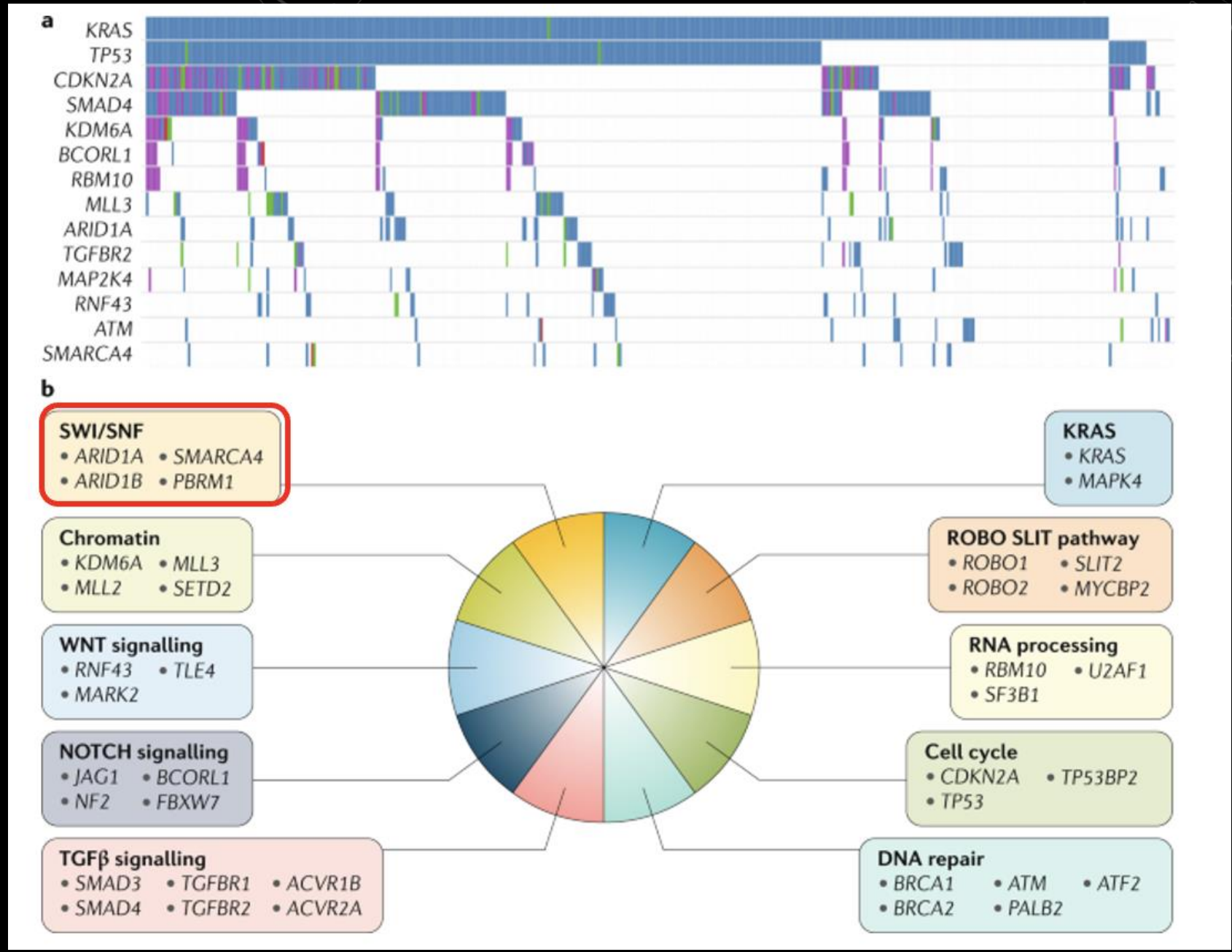
Molecular Targets

ECM Targets

Metabolic Targets

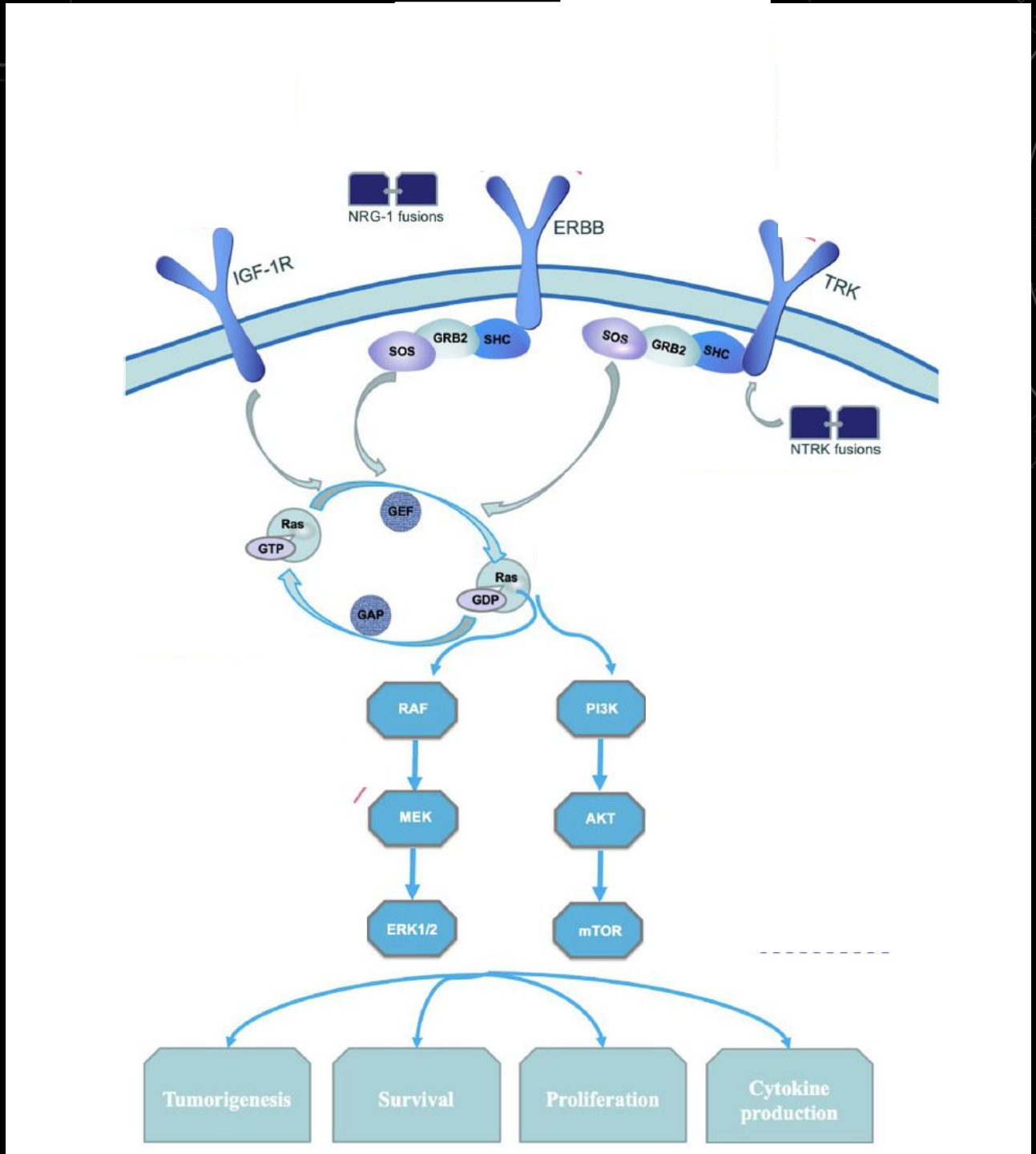
Immune Targets

Hruban et al. 2000
De Santis et al. 2024
Orth et al. 2019



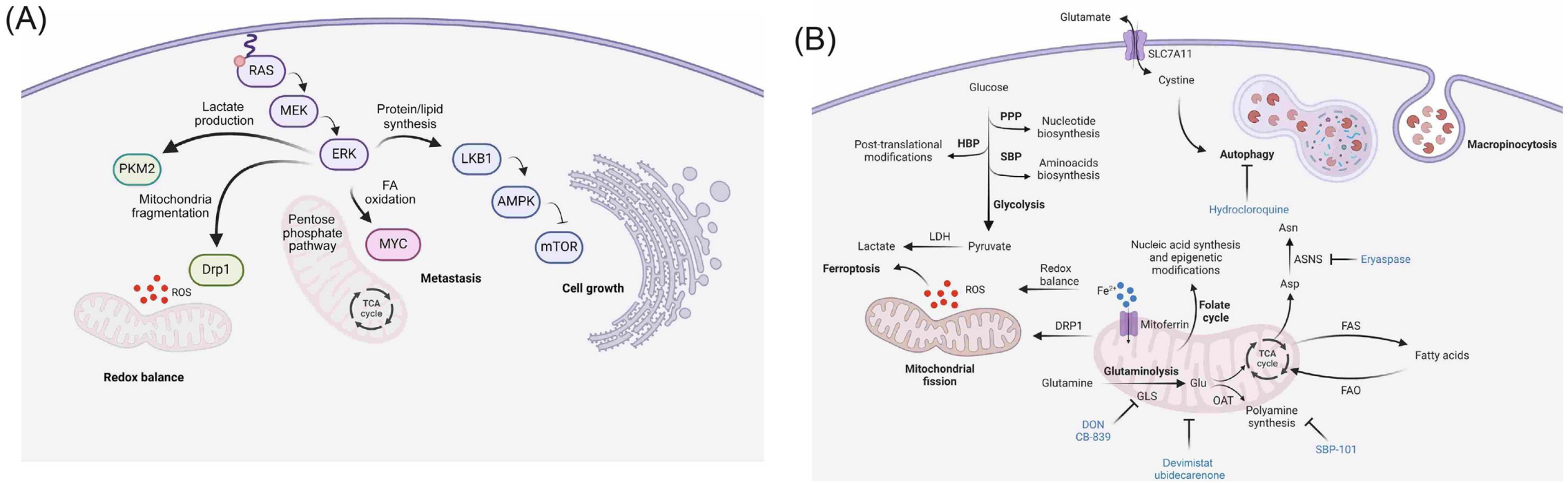
Collison et al. 2019

Pancreatic Cancer: Molecular Signaling of Growth Factors



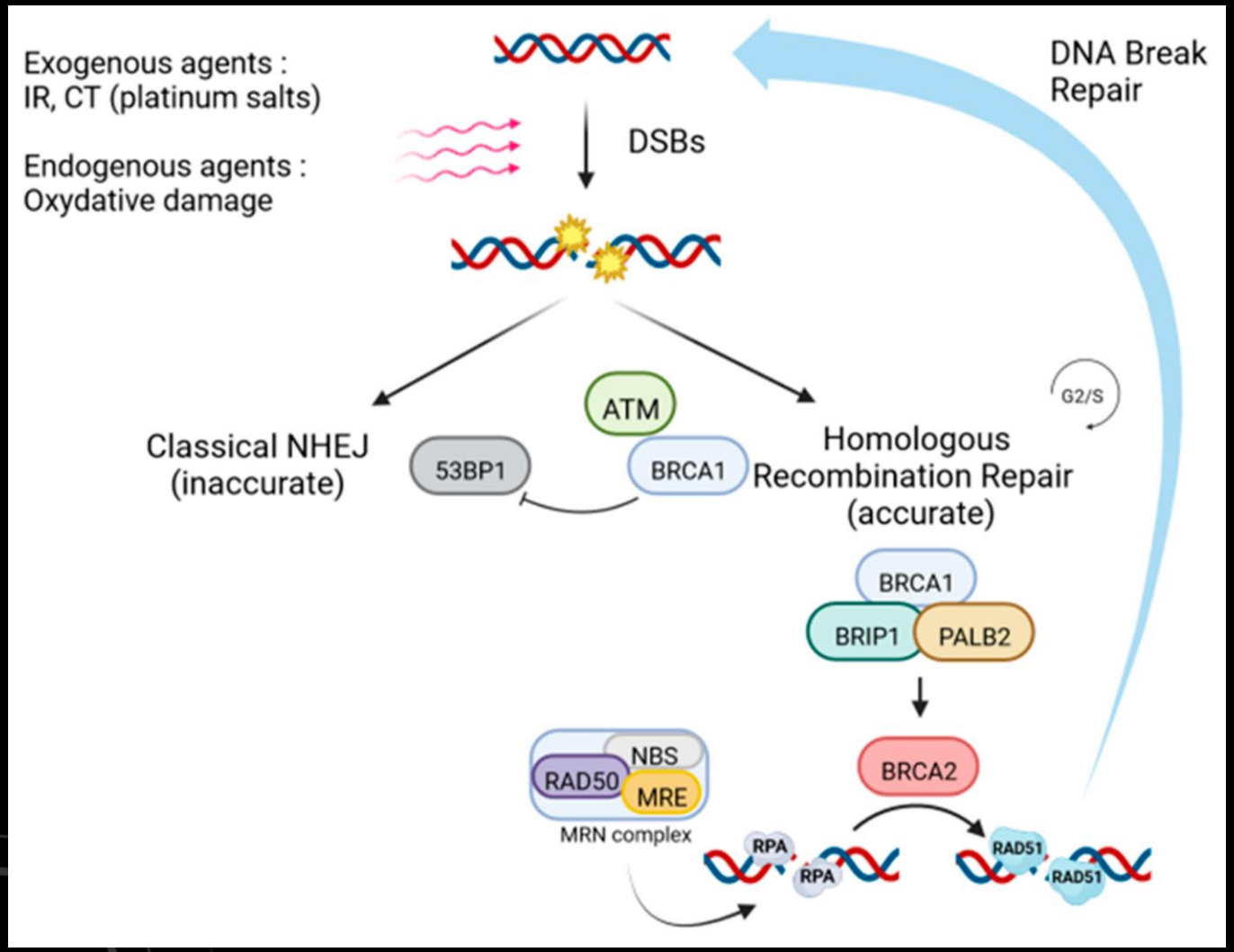
Qian et al. 2020

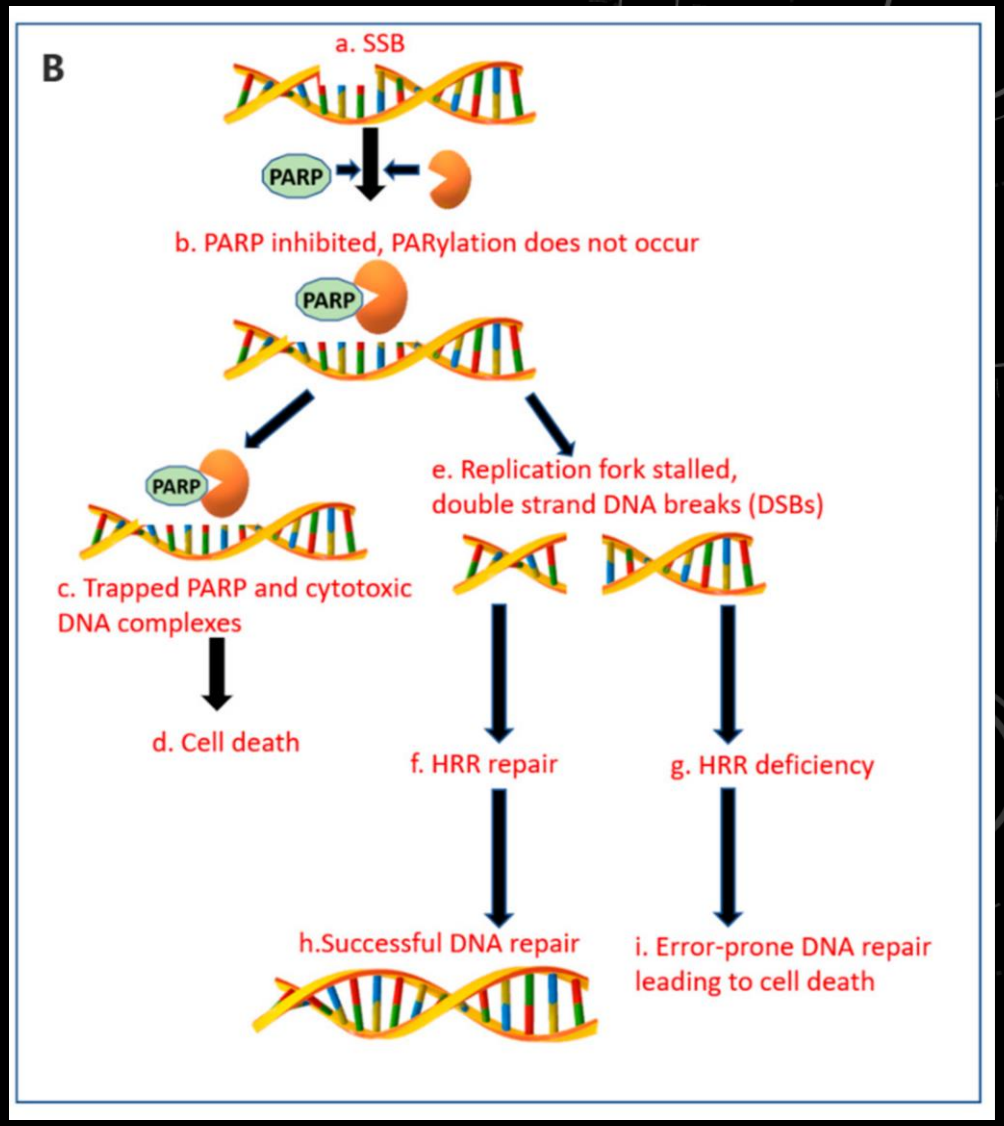
Pancreatic Cancer: Molecular Signaling of Metabolism



De Santis et al. 2024

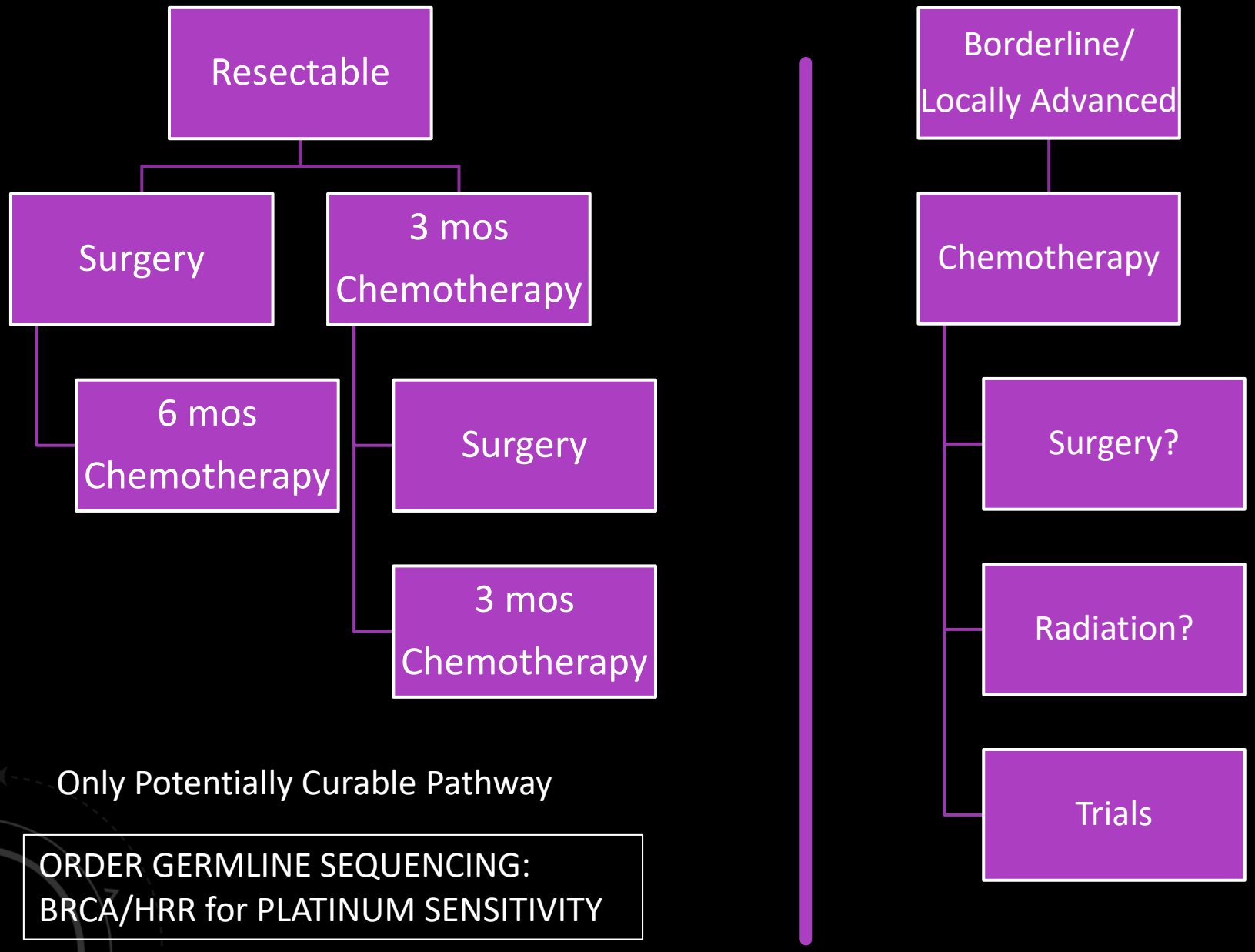
Pancreatic Cancer:
Molecular Signaling of DNA Repair





Ricci et al. 2022

PANCREATIC CANCER CARE 2024



Only Potentially Curable Pathway

ORDER GERMLINE SEQUENCING:
BRCA/HRR for PLATINUM SENSITIVITY

TISSUE:
1. Order Whole Exome Sequencing + ctDNA
2. Order Targeted Gene Panel

BLOOD:
1. Order Targeted Gene Panel

PANCREATIC CANCER: ACTIONABLE TARGETS 2024

Current Pancreatic Cancer Targets

- NTRK
- HER2
- BRAFV600E
- RET Gene Fusion
- BRCA1/BRCA2
- $KRAS^{Wild\text{-}Type}$
- MSI-H
- TMB-H

Future Pancreatic Cancer Targets

- CLDN18.2
- $KRAS^{Mutant}$
- $KRAS^{Wild\text{-}Type}$
- Glutamine/Adenosine
- CD40
- SWI/SNF
- STING
- CSF-1R Inhibitor
- IDO Inhibitors
- iRGD
- Glutamine/Adenosine
- Vaccines

"Failed" Pancreatic Cancer Targets

- Hedgehog
- PEGPH20
- Bruton's Tyrosine Kinase
- CTGFR
- SM-88 + DMS

CURRENT UCSD PANCREATIC CANCER TRIALS PORTFOLIO 7/2024

Resectable

ALLIANCE 021806: A phase III trial of perioperative versus adjuvant chemotherapy for resectable pancreatic cancer

Borderline and Locally Advanced

ARCUS: a pilot study of Zimberelimab and Quemliclustat in combination with chemotherapy

Locally Advanced

CD40 Antibody: IRE + IT Mitazalimab

Metastatic

RMC: KrasG12D Inhibitor (pending)

TAK-500: ADC of STING to CCR2 Ab +/- Pembrolizumab

FORLONG: Long Acting IL-15 agonist

Immuneering: Dual MEK 1/2 Inhibitor

ETCTN 10486: BET inhibitor (ZEN003694) + PARP Inhibitor (Talazoparib)

Solid Tumor CAR-T Trials

BASECAMP-1: HLA-A*02 Heterozygosity for pre-screening study to identify patients for potential treatment in our clinical trials.

EVEREST-1: a phase 1/2, multi-center, open-label study to evaluate the safety and efficacy of A2B530, an autologous logic-gated Tmod CAR T cell therapy.

EVEREST-2: a phase 1/2, multicenter, open-label study to evaluate the safety and efficacy of A2B694, an autologous logic-gated Tmod CAR T cell therapy

TACTIC: a Phase I/II study investigating the safety and efficacy of autologous TAC-T cell asset, TAC101-CLDN18.2, targeting Claudin 18.2+ solid tumors

POSEIDA: a Phase 1, open label, dose escalation and expanded cohort study of P-MUC1C-ALLO1 in adult subjects with advanced or metastatic epithelial derived solid tumors

Abbisko: potent FGFR inhibitor with activity against resistant FGFR mutations

Investigator-Initiated Trials

SWITCH: a Phase 2 open-label trial of Gemcitabine + Cemiplimab in SWI/SNF Altered Metastatic Pancreatic Cancer (pending)

CURE PRIZE: Perioperative Fostamatinib + Chemotherapy for Resectable Pancreatic Cancer (pending)

ORDERING NGS

Targeted Sequencing (Panels)

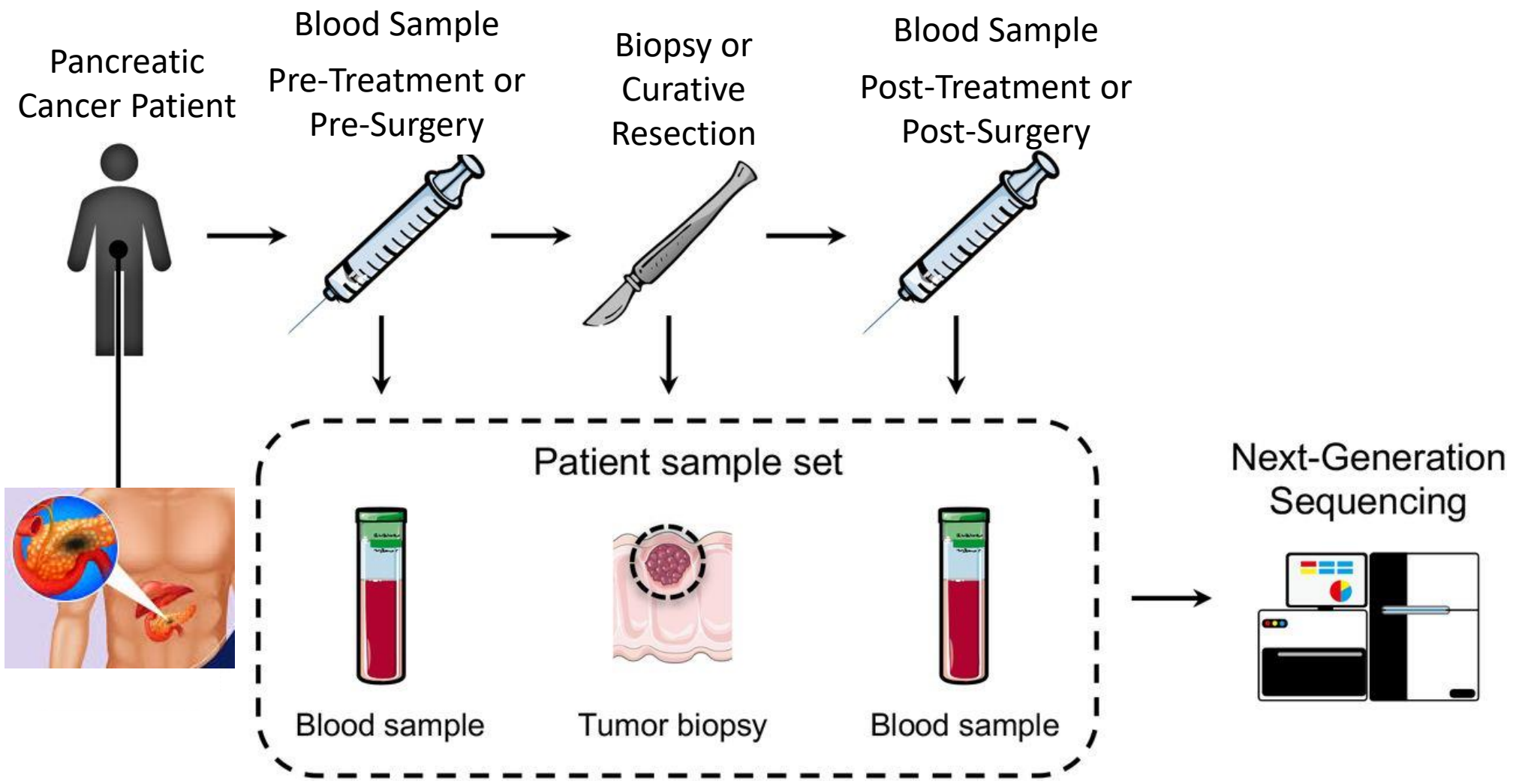
Whole Exome Sequencing (WES)

Whole Genome Sequencing (WGS)

Tissue
Blood

Tissue

Tissue


Pancreatic Cancer Patient
Blood Sample
Pre-Treatment or Pre-Surgery
Biopsy or Curative Resection
Blood Sample
Post-Treatment or Post-Surgery
Patient sample set
Blood sample
Tumor biopsy
Blood sample
Next-Generation Sequencing

PANCREATIC CANCER: NEXT GENERATION SEQUENCING REPORTS

Patient #1: Blood Panel

Diagnosis
Malignant neoplasm of pancreas

xF+

Date of Birth

Sex
Male

Physician
Gregory Botta

Institution
UCSD Health - Moores Cancer Center

TEMPUS | xF+
523 gene liquid biopsy

cfDNA specimen:
Peripheral Blood
Collected 5/29/2024
Received 5/30/2024

NO POTENTIALLY ACTIONABLE VARIANTS AND NO REPORTABLE TREATMENT OPTIONS FOUND.

GENOMIC VARIANTS

Biologically Relevant			Variant Allele Fraction
KRAS	p.G12D	Missense variant (exon 2) - GOF	9.6%
TP53	p.L43fs	Frameshift - LOF	6.3%

ctDNA Tumor Fraction

10.0%

ctDNA tumor fraction is a quantitative measure of circulating tumor DNA.

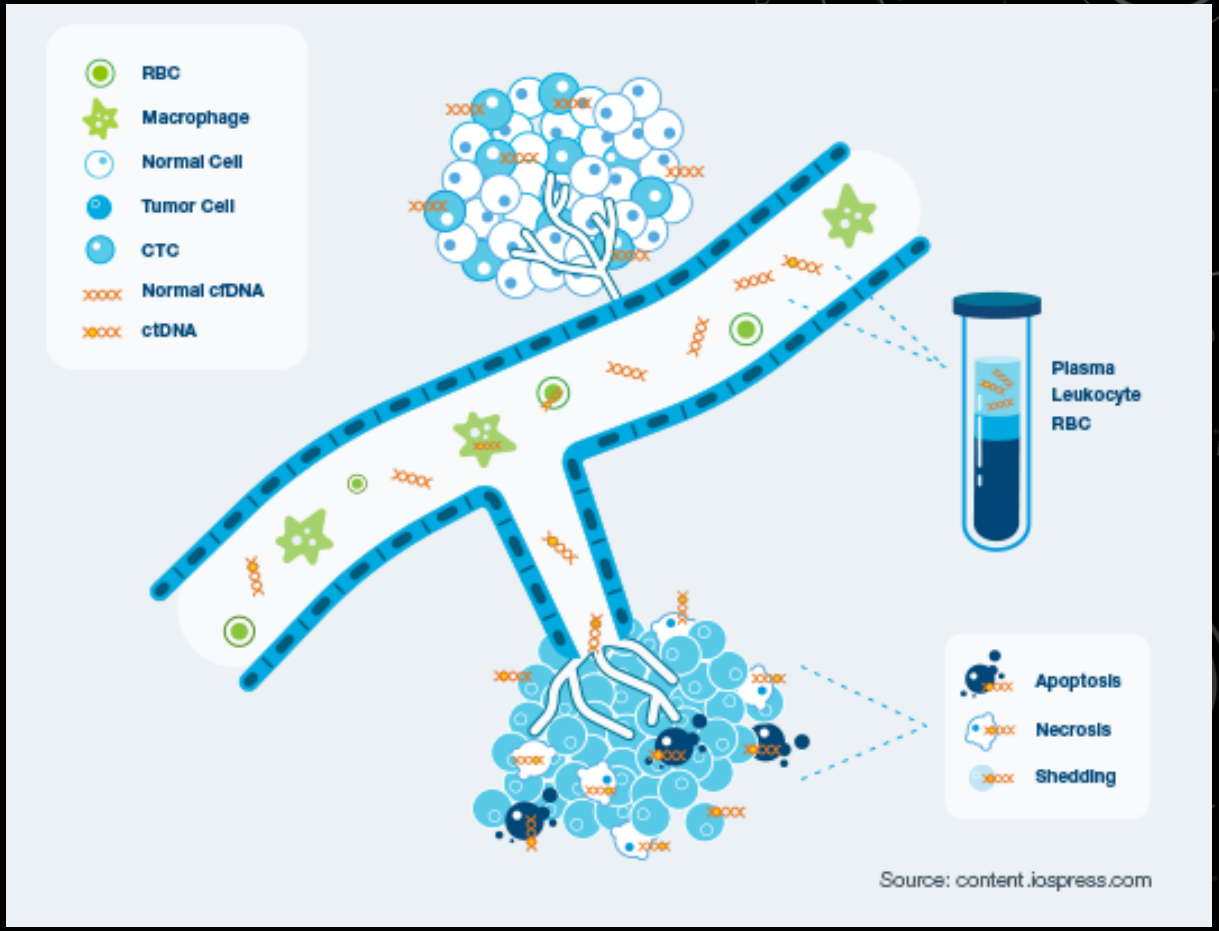
Patient #2: WES

GENOMIC TARGETS	FDA-APPROVED DRUGS -for patient's cancer	FDA-APPROVED DRUGS -for another cancer	DRUGS PREDICTED NON-BENEFICIAL	POTENTIAL CLINICAL TRIALS
18	1	16	0	Yes
ARID1A (K1072fs)				Yes
AXIN2 (A599fs)				Yes
BRCA2 (I605fs) [2]		niraparib, olaparib, rucaparib, talazoparib		Yes
CDKN2A (D84N)				Yes
FANCM (Y622fs)				Yes
KRAS (G12D)		binimetinib		Yes
MLH1 (c.545+1G>A)				Yes
MSH6 (F1088fs)				Yes
MSH6 (F1104fs)				Yes
PPM1D (N512fs)				Yes
PTEN (N323fs)		copanlisib, everolimus, temsirolimus		Yes
RAD50 (N934fs)				Yes
SLX4 (I1478fs)				Yes
SMARCA4 (T1264fs)		tazemetostat		Yes
SMARCB1 (R53*)		tazemetostat		Yes
TP53 (Y220C)				Yes
TUMOR MUTATION BURDEN (TMB)				
HIGH (52 mut/Mb)	pembrolizumab	atezolizumab, avelumab, cemiplimab, durvalumab, nivolumab, nivolumab + ipilimumab		Yes
MICROSATELLITE STATUS (MSI)				
HIGH	pembrolizumab	atezolizumab, avelumab, dostarlimab-gxly, durvalumab, nivolumab, nivolumab + ipilimumab		Yes

CIRCULATING TUMOR DNA

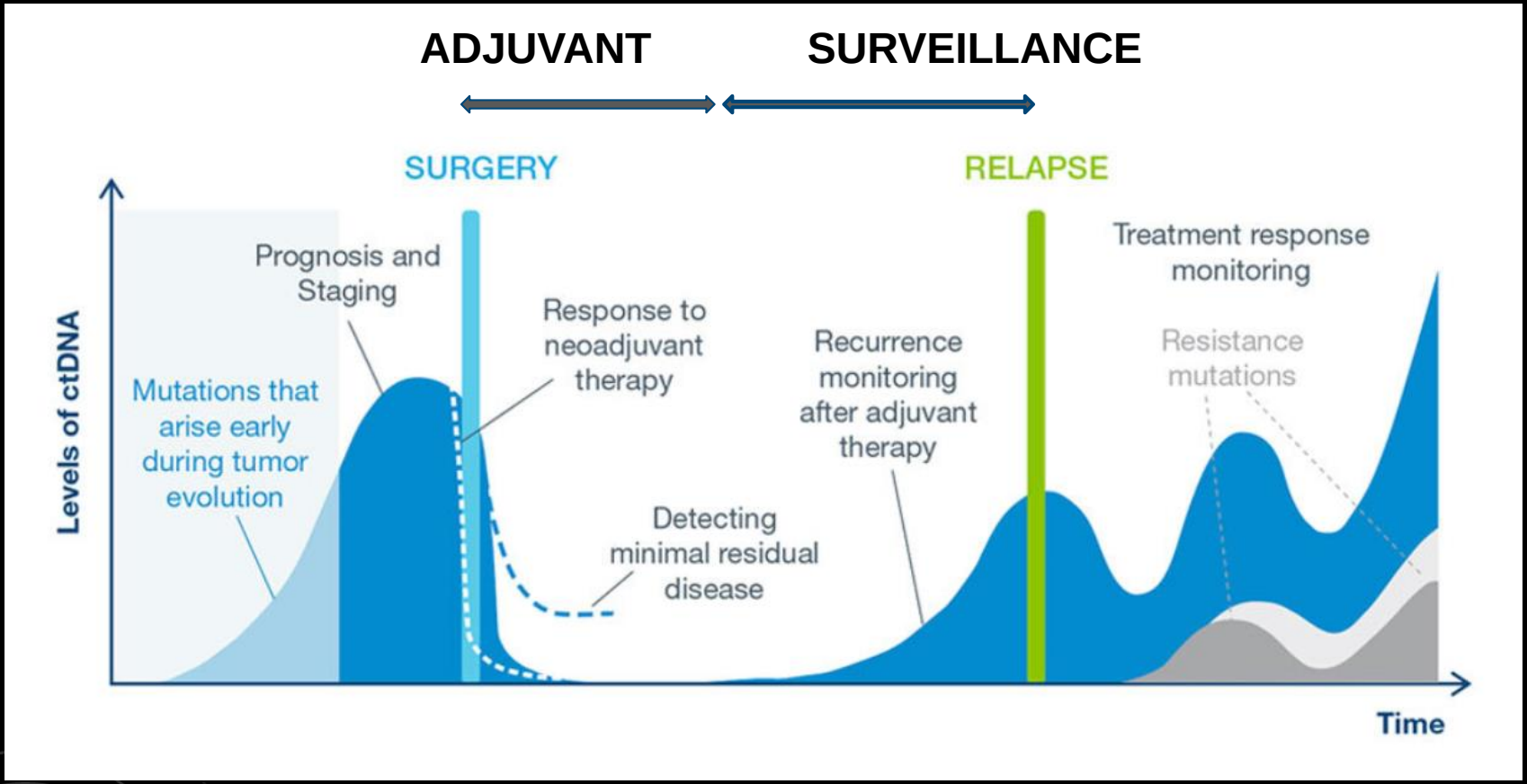
USING CIRCULATING TUMOR DNA FOR MRD ASSESSMENT

- Cancer cells release circulating tumor DNA (ctDNA) into the bloodstream
- ctDNA is a powerful tool that can be measured to assess the absence or presence of molecular residual disease (MRD)
- Dynamic real-time biomarker: the normal half-life is less than an hour



Hahn AW, Nussenzveig RH, Maughan BL, Agarwal N. Cell-free Circulating Tumor DNA (ctDNA) in Metastatic Renal Cell Carcinoma (mRCC): Current Knowledge and Potential Uses. Kidney Cancer. 2019;3:7-13.

CLINICAL APPLICATIONS OF CTDNA TO MEASURE MOLECULAR RESIDUAL DISEASE (MRD)



Common MRD Use Cases

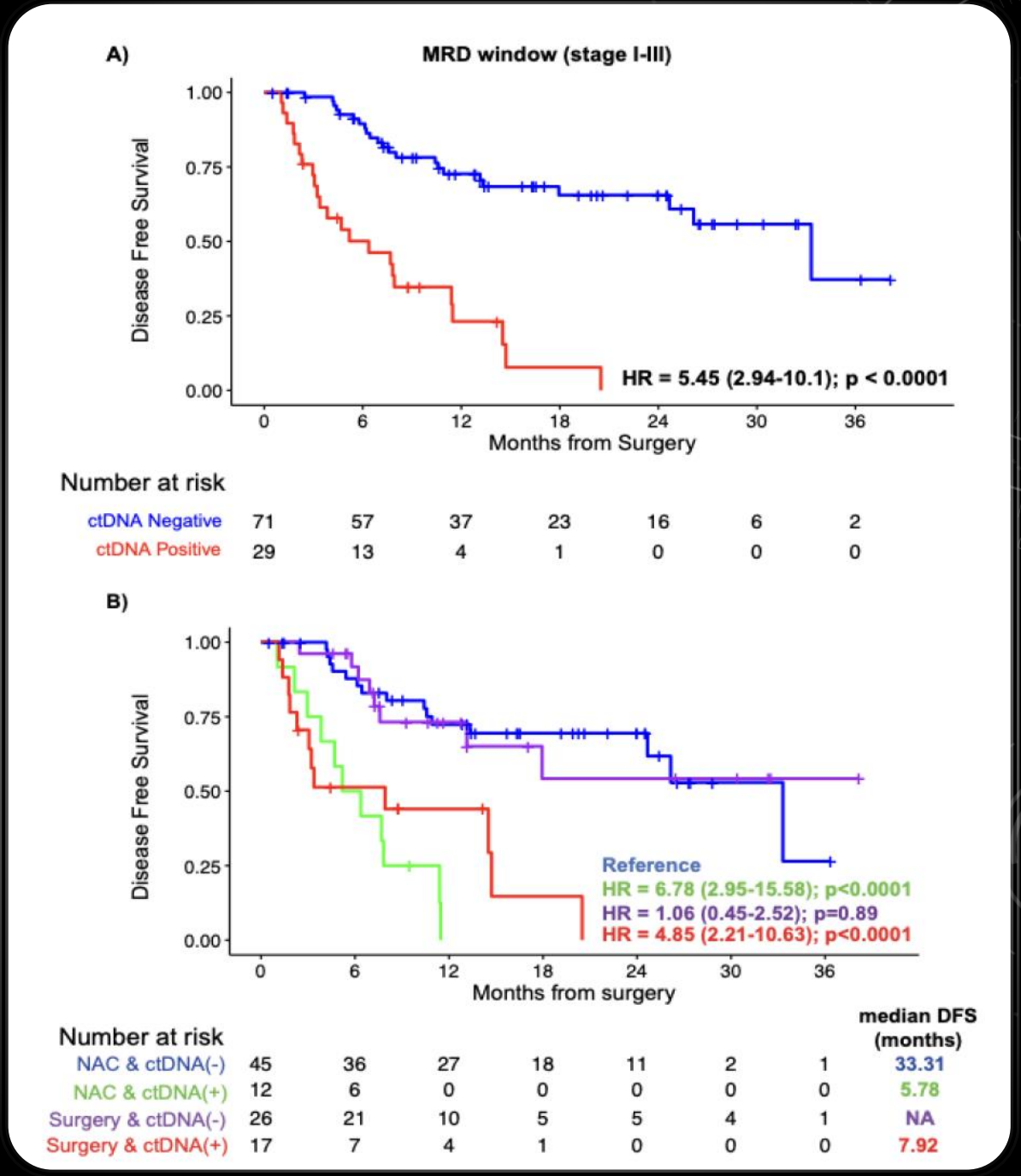
- **A** Post-surgery to inform adjuvant treatment decisions
- **B** Serial testing to rule in / rule out recurrence earlier
- **C** Treatment response monitoring to assess treatment strategies

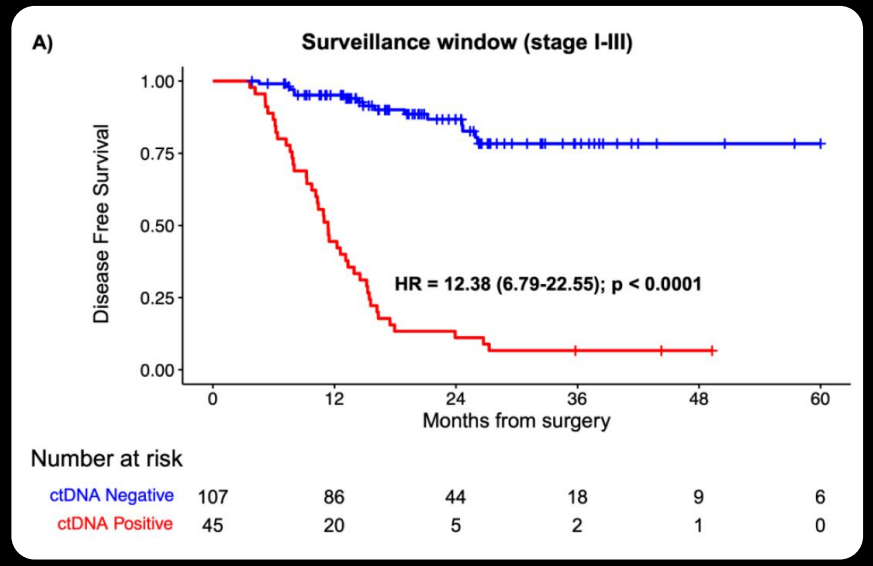
ASSOCIATION OF PERSONALIZED AND TUMOR-INFORMED CTDNA WITH PATIENT SURVIVAL OUTCOMES IN PANCREATIC ADENOCARCINOMA

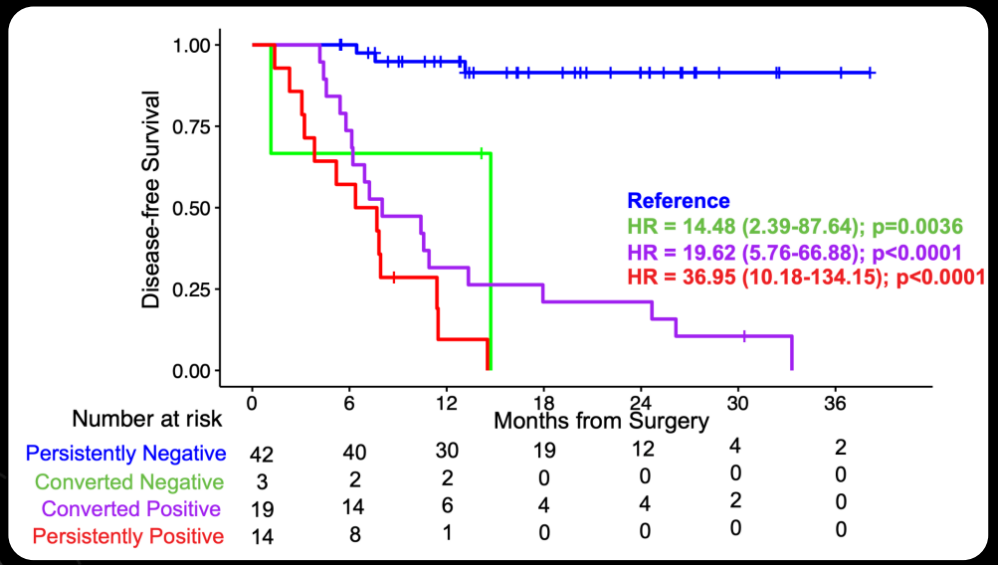
BOTTA ET AL. 2024

PERI-OPERATIVE

- ctDNA Negativity has less disease recurrence and improved prognosis after Neoadjuvant chemotherapy or surgery in pancreatic cancer







SURVEILLANCE

- Persistent ctDNA Negativity after curative intent therapy has less disease recurrence and improved prognosis for patients on surveillance

Pancreas Cancer

- Diagnostic vs Informative Biopsy
- Previous Tissue or new blood

Clinical Integration

- Choose Targeted Therapy
- Select Clinical Trial
- Avoid Non-Responsive Treatment

Liquid NGS/ctDNA

- Evaluate allele fluctuations over time
- Target reduction or increase

Assay Type

- Blood/Tissue Panel
- WES
- WGS

Genomic Databases

- Actionable Mutations
- VUS
- Prognostic/Predictive

Monitor Response/Resistance

- Dynamic ctDNA changes
- Dynamic Clonal Evolution
- New/refractory Mutations

Order

- Formalin Fixed
- Fresh Frozen
- Blood
- ctDNA: Germline, Somatic

Bioinformatics

- Align Genome
- Call SNPs
- Multiplex Signatures

Clinical Decision Making

- Continue therapy
- Taper intensity
- Increase Intensity
- Change Therapy