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COMPREHENSIVE CANCER CENTER

Treatment Approaches for Pancreatic Cancer: Hope on the Horizon

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NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

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Disclosures

- Consultant
  - Bayer/Onyx
  - Sirtex
- Chief Medical Officer
  - Personalized Cancer Therapy, Inc

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Outline

- Background
- Surgery
- Medical Therapy
  - Post-surgery (adjuvant therapy)
  - Locally advanced
  - Metastatic
- New Trials and New Promise

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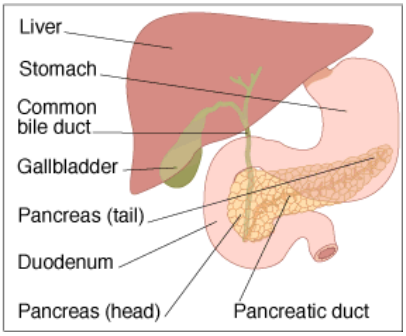
Pancreatic Cancer

- US in 2012
  - 43,920 new diagnoses
  - 37,390 deaths
- Worldwide in 2008
  - 278,684 new diagnoses
  - 266,669 deaths



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Risk Factors

- Tobacco and Alcohol Use
  - Minor
- Genetically Inherited (<5%)
  - BRCA1 & 2
  - PALBB2
- Other Causes
  - Chronic Pancreatitis
  - Toxins (very, very rarely)
  - Race?
  - Diet?

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Symptoms

- Abdominal pain
- Weight loss
- Jaundice/Biliary Obstruction
- Fatigue
- Dyspepsia
- Diabetes Mellitus

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Difficulties in Assessment

- Subtle symptoms
- Hard to visualize
  - CT vs. MRI
  - Endoscopic ultrasound
  - Unclear role of PET scans
- Nature of spread/metastases
  - Ascites
  - Lymph nodes
  - Local spread/invasion
  - Distant metastases

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Can We Diagnose it Earlier?

- No evidence for CTs, MRIs, EUS, etc
  - *Not even in the rare families with inherited pancreatic cancer*
- Is there a blood test?
  - *Ca 19-9 is not a useful screening tool*
  - Serum microRNA? Metabolomics?

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Pancreatic Cancer Staging

- Stage I:
  - IA: T1, N0
  - IB: T2, N0
- Stage II
  - IIA: T3, N0
  - IIB: T1-3, N1
- Stage III: T4, N any (locally advanced, unresectable)
- Stage IV: T any, N any, M1

- **Primary Staging is Resectable vs. Unresectable**
  - **Secondary – Locally Advanced vs. Metastatic**

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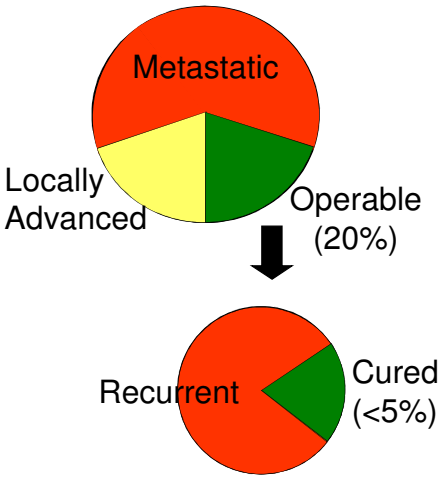
Pancreatic Cancer Statistics

- Pancreatic cancer can be a deadly disease
- At diagnosis
  - Only 20% are operable
  - 20% are inoperable, locally advanced
  - 60% are metastatic
- For the 10-20% who are operable
  - 80% will recur
  - 20% will be cured (<5% overall)



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Surgical Definitions

- Whipple Procedure for head/body of pancreas tumors
  - Removes head and body of pancreas, duodenum, part of stomach (sometimes), gall bladder (usually)
  - Major operation – 4-6 week recovery
  - Change in digestion ("plumbing") after
  - "Lap-assisted" Whipple – revolutionary
- Distal pancreatectomy – for tail of pancreas tumors
  - Removes tail of pancreas
  - Spleen (shared blood supply)
  - Less-major operation ~4 weeks of recovery
  - Laparoscopic distal pancreatectomies

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Surgical Definitions

- Common surgical principles
  - Assessment of vasculature
    - Tumors involving arteries might not be remove-able
    - Tumors involving veins – more controversial
  - Assessment of peritoneum and liver
  - Removal of tumor with good "margins"
  - Removal of local lymph nodes

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Recovery from Surgery

- Usually takes 4-6 weeks
- Often includes surgical drains
- Infections can occur
- Adjusting to new “plumbing”
- Patients often lose 10-20% of their body weight (forever)

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Medical Therapy: Outline

- Post-operative
  - “Adjuvant”
  - Decrease rates of recurrence = increased cure
  - “Neoadjuvant”
- Locally Advanced
  - “Conversion” therapy
  - Slow development of metastases
  - Extend survival
  - Maintain quality of life
- Metastatic
  - Extend survival
  - Maintain quality of life

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Post-Operative Therapy

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Post-Operative Therapy

- Only 20% of *operable* patients are cured
  - Average survival ~24 months
- 80% chance of recurrence after surgery
  - Local and systemic recurrence
- Pancreas cancer "seeds" very early
  - Can we kill those seeds?

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Post-Operative Chemotherapy

- Clear benefit
  - Prolonged survival
  - Decreased recurrence = increased cure
- Examples
  - ESPAC-1 (5-Fluorouracil vs. observation)
    - Average survival: 20 vs. 15 months
    - % 5 year survival: 21 vs. 8%
  - CONKO-001 (Gemcitabine vs. observation)
    - Average survival: 22 vs. 20 months
    - % 5 year survival: 17 vs. 6%

Saif, JOP. 2009 Jul 6; 10(4):373-377.

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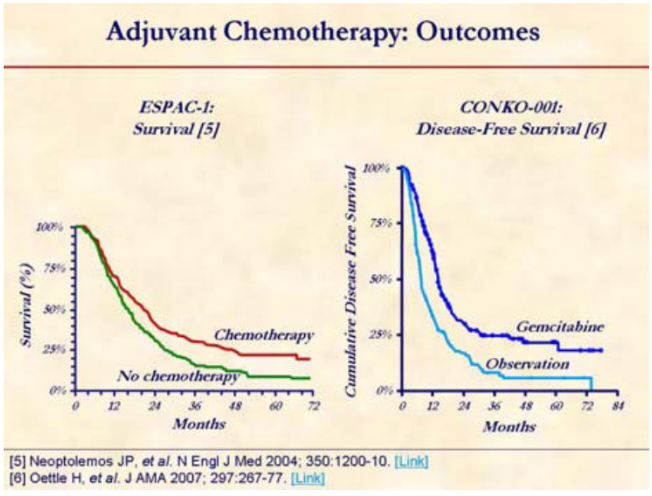
Post-Operative Chemotherapy



Saif, JOP. 2009 Jul 6; 10(4):373-377.

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Post-Operative Chemotherapy

- What kind of chemotherapy
  - ESPAC-3: Gemcitabine vs. 5-Fluorouracil
  - Average Survival: 23.6 vs. 23 months
- Benefit of radiation?
  - Not clear
  - Radiation (with a low dose of oral 5-Fluorouracil) for 4-6 weeks after chemotherapy

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Neoadjuvant Therapy

- For patients with resectable disease
  - Prior to surgery
  - Chemotherapy +/- radiation
- Are we just selecting patients out?
  - Overall survival still ~24 months
  - 30% of patients – surgery not appropriate
    - Patients become ill
    - Cancer grows/spreads before surgery
  - Of the remaining 70%
    - Improved overall survival
    - 30-34 months
- Highly debated topic
  - Should be pursued as a randomized trial

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Locally Advanced Disease

Definitions

Respectable vs. Unresectable: Definitions Vary

- Resectable disease
  - No involvement with local blood vessels
- Borderline resectable disease
  - Abutment (<180º) of the local arteries
- Unresectable disease
  - Encasement (>180º) of the local arteries
- Involvement of the veins – greater variation

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Locally Advanced Cancer

- Chemotherapy PLUS Radiation
  - Clearly improves survival over radiation alone
  - Average survival ~12 vs. 6 months
- Is radiation necessary?
  - Controversial due to mixed results

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Locally Advanced Cancer

- Sequence of therapy?
  - Radiation first
    - ~30% will develop metastases just after radiation
  - Chemotherapy first
    - ~30% will have growth of the primary mass, even if there are no metastases
- Type of radiation?
  - Traditional or IMRT?
  - Stereotactic radiation?

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Disease "Conversion"

- Making unresectable disease → resectable
  - Only occurs in 10-20% of patients (at most)
- Choice of chemotherapy?
  - Better outcomes with FOLFIRINOX?
- Choice of radiation?
  - Traditional or IMRT vs. Stereotactic radiation

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Metastatic Disease

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Metastatic Cancer: Pre-2011

- Average survival
  - No treatment 2-4 months
  - With chemotherapy 6-8 months
  - 1 year survival rate ~ 20%
- Goal of therapy
  - Extend survival
  - Improve symptoms

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Metastatic Cancer: Pre-2011

- Gemcitabine
  - Very well tolerated
  - Initially approved based on an improved quality of life
- Survival benefit vs. 5-Fluorouracil
  - Average survival 5.7 months vs. 4.4 months
  - 1 year survival 18% vs. 2%

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Combination Chemotherapy?

- No chemotherapy with gemcitabine had been proven to be superior to gemcitabine alone in survival
  - 5-FU/capecitabine
  - Oxaliplatin/Cisplatin
  - Irinotecan
  - Pemetrexed
- Example: Gem + Oxaliplatin vs. Gem alone
  - Increased response rate with Gem + Ox
  - BUT survival rates the same
- What about targeted therapies?

Poplin, JCO. 2009 Aug 10;27(23):3778-85

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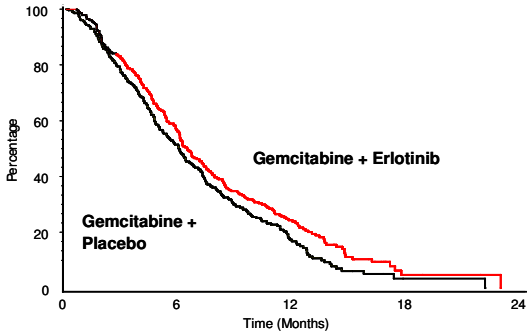
Only One Targeted Therapy

- Gem vs. Gem + erlotinib – Phase III
- Average survival 6.37 months vs. 5.91 months
  - .46 months = 14 days
- 1 year survival 24% vs. 17%



Moore, JCO 2007

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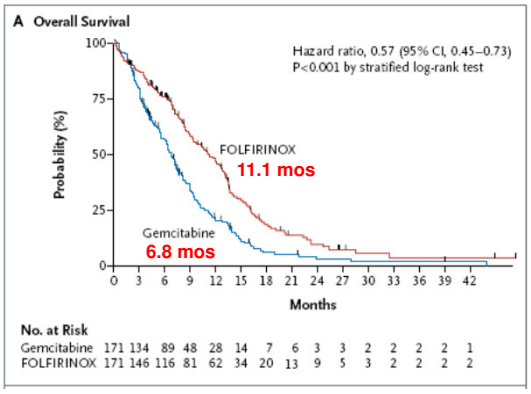
New Standards – Post-2011

- FOLFIRINOX vs. Gemcitabine - Phase III
  - RR: 31% vs. 9%
  - OS: 11.1 vs. 6.8 mos
  - Moderate toxicity



Conroy, *et al*, NEJM, 2011, 364;19

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New Standards – Post-2011

- Gemcitabine + *nab*-paclitaxel vs. Gemcitabine
  - Phase III
  - Well tolerated

Gemcitabine		Gemcitabine/ nab-Paclitaxel
6.7 months	Median Survival HR=0.72, P=0.000015	8.5 months
22%	1-year Survival	35%
4%	2-year Survival	9%
3.7 months	Median Progression Free Survival HR=0.69, P=0.000024	5.5 months
7%	Overall Response Rate	23%
33%	Stable Disease	48%

Von Hoff, et al, ASCO, 2013

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New Hope on the Horizon

Clinical Trials in Pancreatic Cancer

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Metastatic → Earlier Stage

- Can we apply metastatic regimens to localized disease
  - Locally advanced/borderline resectable
    - Increase rate of resectability
    - Pre-op FOLFIRINOX or Gem + *nab*-paclitaxel
  - Adjuvant therapy
    - Increased eradication of micrometastatic disease
    - Adjuvant FOLFIRINOX or Gem + *nab*-paclitaxel

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Improved Local Therapy

- Stereotactic radiation
- Irreversible electroporation
- Liver-directed therapy

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New Treatments

- New targets being identified
  - Targeting the cell surface
  - Targeting cell signaling
  - Targeting cell division
  - Targeting the tumor environment
  - Immunotherapy

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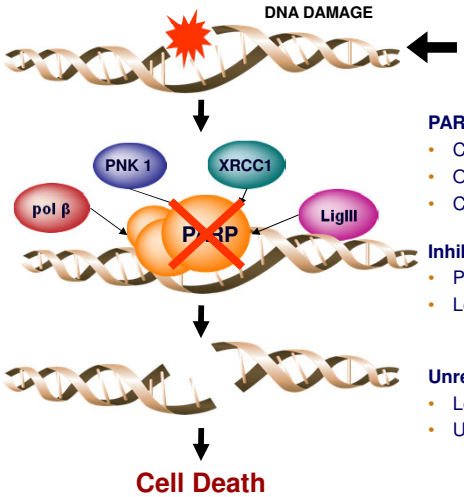
New Targets: PARP



Chemotherapy
(e.g. alkylating agents)
Radiotherapy

Environmental factors
(UV, radiation, chemicals)
Normal physiology
(DNA replication, ROS)

PARP
- Critical DNA repair enzyme (SSB, BER)
- Often overexpressed in cancer cells
- Confers resistance to chemotherapy and radiation

Inhibition of PARP
- Prevents recruitment of DNA repair enzymes
- Leads to failure of single strand break repair

Unrepaired break site → replication fork arrest
- Leads to degeneration into double-strand breaks
- Ultimately → chromosomal catastrophe cell death

Tutt, A, et al, JCO /ASCO, 2009
Helleday T, et al. Nat Rev Cancer, 2008

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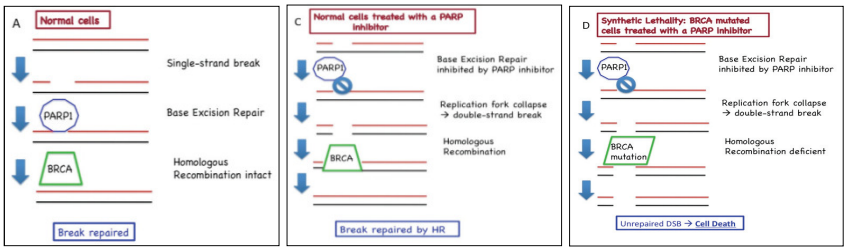
Homologous Recombination Deficient Cells Are More Susceptible to PARP Inhibition

- BRCA-1, -2 are critical for DNA repair via HR
- Cells defective in BRCA-1, -2 are more sensitive to DNA-damaging therapy
- Cells defective in BRCA-1, -2 are more sensitive to PARP inhibition
  - Cancer cells unable to repair double-stranded breaks die through apoptosis



Rowe and Glazer Breast Cancer Research 2010, 12:203

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Homologous Recombination Deficient Cells Are More Susceptible to PARP Inhibition

- Homologous recombination enzymes are critical for DNA repair
  - Defects in BRCA-1, -2, PALB-B2, FANC → increased sensitivity to DNA-damaging chemotherapy and to PARP inhibition
- BRCA-2 mutations in pancreatic cancer
  - 5 – 17% of pancreatic cancer patients carry BRCA-2 mutations
- Multiple clinical trials of PARP inhibitors
  - Consistent evidence of increased efficacy in BRCA-1 or -2 mutant tumors
  - Anecdotal evidence in pancreatic cancer
    - e.g. Lowery, *et al*, 2011, MSKCC - 15 patients with known BRCA-1 or -2 mutations
      - » 4 patients with PARPi-based therapy
      - » 3PRs and one SD for 6 months

Rowe and Glazer Breast Cancer Research ,2010
Goggins, M, Cancer Res 1996
Murphy KM, Cancer Res 2002
Ozçelik, H, Nat Genet 1997
Lowery, et al, Oncologist, 2011

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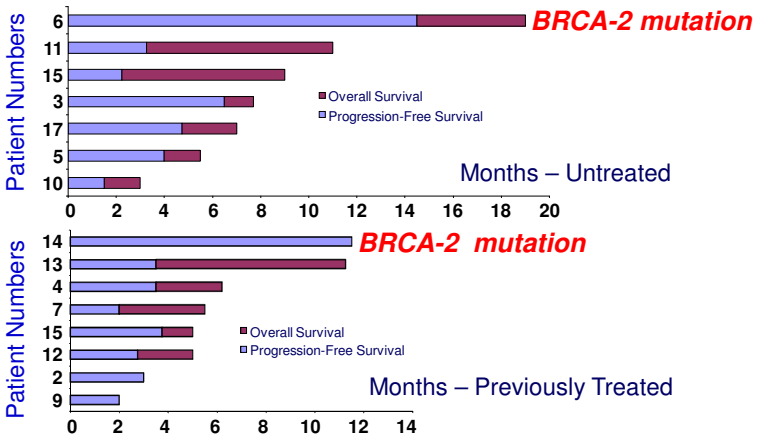
Preliminary Results



- **2 patients with defined *BRCA2* mutations**

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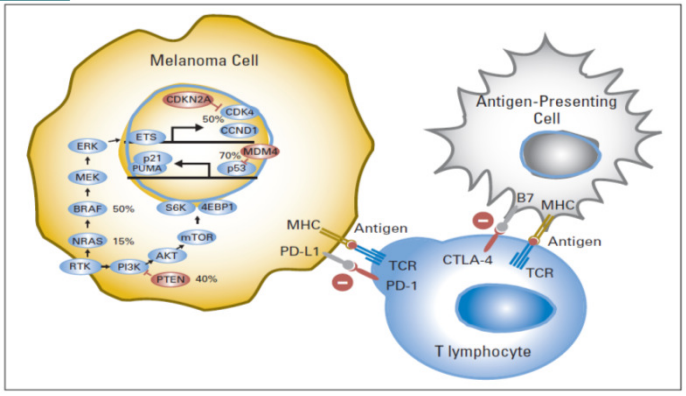
Enhancing Anti-Tumor Immunity



- CTLA-4 is a negative costimulatory molecule
- Blockade of CTLA-4 → Tcell activation and proliferation
- 15 – 20% risk of clinically significant inflammatory and autoimmune adverse effects
- The programmed death 1 (PD-1) receptor is also a negative regulator of T cells
- The PD-1 ligand (PD-L1) is expressed by tumor cells directly
- PD-1 inhibition → direct activation of cancer-specific T-cells with much fewer AEs

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McArthur, GA and Ribas, A, 2013, JCO 31:499-506

M1

Enhancing Anti-Tumor Immunity

- Anti-PD-1 and PD-L1 Abs being tested
- Experience limited
  - Some early evidence of activity in pancreatic adenocarcinoma
  - Very few side effects

Tabernero, et al, ASCO, 2013

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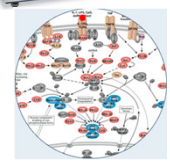
Patient "Tailored" Therapy

New genomic and proteomic tests provide specific information on cancer behavior



Theranostics Health, Inc:
TheraLink™ Drug Target Activation Mapping

Foundation Medicine:
Full Exon Sequencing
Broad-scale mutation analysis
Future: Full Genomic Sequencing

Caris, Inc:
Target Now Assay
IHC and DNA mutations

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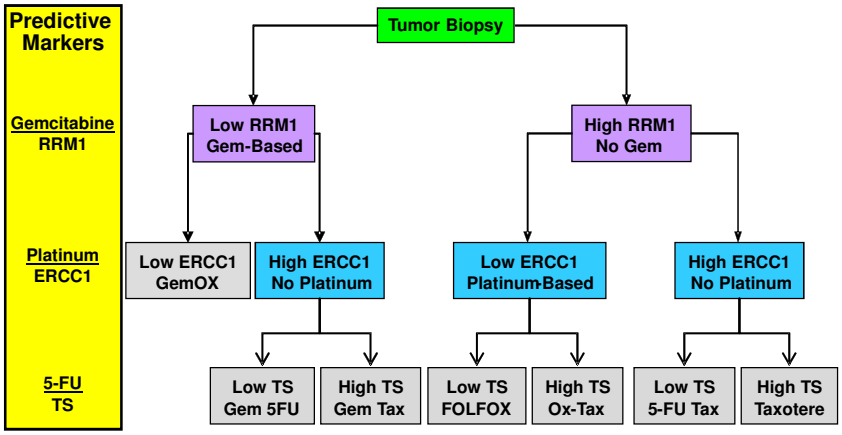
Slide 43

M1 Michael, 11/22/2013

Patient "Tailored" Therapy



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Patient "Tailored" Therapy

- ESMO, 2013 – Hidalgo's group
  - Molecular Profiling → Increased Survival
  - Retrospective Review
  - TS and TP were the strongest predictors
  - OS
    - Profiled patients = 12 months
    - Non-profiled patients = 7.6 months
- AACR, 2012 – Ramanathan's group
  - Prospective study
  - Molecular Profiling → Therapy recommendations in 47 patients

J. Rodriguez-Pascual, et al, ESMO, 2013
Ramanathan RK, et al, AACR 2012, Abstract nr LB-221

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Slide 46

M1 Michael, 11/22/2013

Patient "Tailored" Therapy

- Tumor xenograft model
  - Tumor specimens grown in mice
  - Chemotherapy testing to identify effective treatments
  - Champions Oncology
- Pharmacogenomics model
  - Serum testing of tumor-borne chemosensitivity markers
  - CellPath Therapeutics

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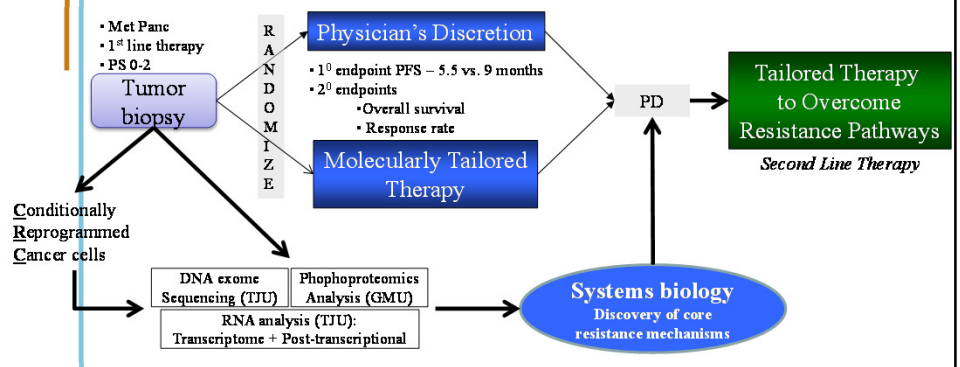
Patient "Tailored" Therapy



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Pancreatic Cancer - The Future

- Can we diagnose patients earlier?
- Can we operate on more patients?
  - Preoperative studies – RENDER more patients operable
- Postoperative Therapy
  - Decrease chance of recurrence
- New Therapies
  - We desperately need novel clinical trials
- Personalized Therapy
  - Can we treat each patient with the therapy they need?
  - Can we apply this to the adjuvant/pre-operative setting?

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Thank You

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