Metastatic Pancreatic Cancer
Yale Pancreas Day

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Yale School of Medicine
**FOLFIRINOX vs gemcitabine**

- **5-FU**
- **Oxaliplatin**
- **Irinotecan**

**Overall Survival**
- Hazard ratio, 0.57 (95% CI, 0.45–0.73)
- P<0.001 by stratified log-rank test
- **11.1 mo vs 6.8 mo**

**Progression-free Survival**
- Hazard ratio, 0.47 (95% CI, 0.37–0.59)
- P=0.001
- **6.4 mo vs 3.3 mo**
Gemcitabine and nab-paclitaxel vs gemcitabine

8.5 mo vs 6.7 mo

5.5 mo vs 3.7 mo
Which Regimen to Use First Line?

VS
mFOLFIRINOX

- Modifications can make the regimen more easy to tolerate
  - (lowering irinotecan dose, decreasing 5-FU bolus)

- Growth factor support
- Antiemetics
Liposomal Irinotecan

Nanoliposomal encapsulation of irinotecan (NAPOLI-1)

417 patients after gem or gem-based therapy

Liposomal irinotecan or 5-FU/LV or the combination

Wang-Gillam Lancet 2016
NAPOLI-1

mOS = 6.1 mo for comb vs 4.2 mo 5-FU/LV

PFS = 3.1 mo vs 1.5 mo
Pancreatic Cancer Microenvironment

- High tumor interstitial pressure
- Compression of tumor blood vessels
- Hypoxia
- Protumorigenic growth factors and cytokines accumulate in the HA-rich tumor ECM
- Limited access of systemic therapies

Tumor
- ↓ Tumor interstitial pressure (19)
- ↑ Vascular/tumor perfusion (16, 40)
- ↓ Hypoxia (17)
- ↑ Access of systemic therapies to the tumor accompanied by increased efficacy (16, 40, 41)

Tumor Extracellular Matrix
- Depletion of HA, remodeling of the TBM (16, 17, 40, 41)
- HMW HA ★ LMWH, HA, HA fragments released into the circulation as a result of systemic/tumor HA depletion (42), leading to decreased tumor IP
- Possible release of protumorigenic cytokines and growth factors

Malignant and Tumor Stromal Cells
- Activation of CD44/RHAMM signaling and ↓ tumor growth (43)
- ↓ EMT/metastasis (17)
- Possible that HA depletion may decrease available precursors for glycolysis thereby contributing to growth inhibition by PEGPH20 (44)

Shepard 2016
PEGPH20 – Stroma Remodeling

A. Baseline

\[ P_i > P_e \text{ and diffusion and convection limited} \]

B. PEGPH20

\[ P_i < P_e \text{ and diffusion and convection favorable} \]

C. Gem+PEGPH20

\[ P_i < P_e \text{ and permanent remodeling of the tumor microenvironment} \]

Provenzano et al
Cancer Cell 2012
PEGPH20 HALO 202

**A** PFS - all

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**B** PFS-HA high

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PEGPH 20 – SWOG 1313

SWOG 1313 – randomized Phase II study

FOLFIRINOX +/- PEGPH20 – stopped after interim analysis showed lack of benefit. HA data not available

Patients receive 2 doses of PEGPH20 in 4 weeks, gem/nab-paclitaxel trial pts received 6 doses in 4 weeks
HALO 301 Study

Screen for HA high tumors – requires core biopsy

Consent if HA high

PEGPH20 + Gemcitabine and nab-paclitaxel

Gemcitabine and nab-paclitaxel
BRCA 1 and 2 Mutations

• Approx 5-10% of patients

• May or may not have a family history

• Paradigm shifting from only testing based on ethnicity
Rationale for PARP Inhibitors

PARP Inhibitors: Mechanism

- PARP and BRCA1/2 normally function to repair daily DNA damage.
- Allows cells to grow in a healthy way.
- Too much DNA damage -> cell death.
- If BRCA1/2 is damaged or not working, the cell is dependent on PARP for all DNA repair.
- PARP inhibitors prevent DNA repair in cancer cells:
  - May increase cancer cell death.
  - May help chemo and radiation work better.

BRCA mutations

• POLO study – PDAC pts with BRCA1/2 mutations - olaparib after platinum chemo combination

• Are there additional patients who are BRCA-like?
Mesothelin

- Tumor-differentiation antigen
- High expression in pancreatic cancer
- Approaches to target MSLN:

Hassan JCO 2016
Anetumab Ravtansine

Antibody-drug Conjugate:

Anti-mesothelial Ab linked to Maytansinoid tubulin inhibitor DM4

- Target antigen should be highly expressed on tumour cells with limited expression on healthy tissues
- Antibody should have high affinity and avidity for tumour antigen
- Stable in circulation
- Must efficiently release the cytotoxic agent inside tumour cell
- Highly potent since only a limited number of molecules can be attached to the antibody
Morpheus Study

- Multiple Immunotherapy Based Combinations in Pts with Metastatic PDAC
- Gemcitabine and nab-paclitaxel
- FOLFOX
- Atezolizumab plus Cobimetinib (MEK inhibitor)
- Atezolizumab plus PEGPH20
- Atezolizumab plus BL-8040 (CXCR4 antagonist)

- Primary Outcome: RR by RECIST, AE
Immune Therapy

- Pembrolizumab approved for MSI-high tumors – but only 1-2%
- What about the rest?
- “MSI-ness”
- Other hypermutation phenotypes (eg POLE mutations)
- Multiple ongoing trials – chemo plus immune therapy
Multidisciplinary Approach

- Medical Oncology
- GI
- Surgical Oncology
- Radiation Oncology
- Nutrition
- Social Work
- Care Coordination
- Palliative Care
In Summary

• Prognosis has only shifted modestly, but multiple studies are underway

• Clinical trial participation is essential!