PERSONALIZED / PRECISION MEDICINE IN ONCOLOGY

Development of Biomarkers and Targeted Therapies

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DISCLOSURES

- Univ California: Patents
- Genentech: Speakers Bureau
- Pfizer: Speakers Bureau
- Merrimack Pharma: Equity
Personalized / Precision Medicine

Themes

• Diagnosis -> Biomarker defined
• Therapy -> Targeted
• Impact -> Translational
Herceptin: Humanized Anti-HER2 Antibody

- Targets HER2 oncoprotein, which occurs in 25% to 30% of patients with breast cancer
- High affinity (\(K_d = 5\text{nM}\)) and specificity
- 95% human, 5% murine
  - Decreased potential for immunogenicity
  - Increased potential for recruiting immune effector mechanisms

Carter et al, 1992; Park et al, 1993; Slamon et al, 1987; Genentech, data on file
HER2 Immunohistochemistry (IHC): (e.g. HercepTest®)

- Pre-analytical tissue processing
- Reagent variability
- Antigen retrieval
- Scoring

0

1+

2+

3+
Fluorescence In Situ Hybridization (FISH)

• Measures the level of HER2 gene amplification
• Normalization to chromosome 17 centromere

<2.0 not amplified (FISH−)

≥2.0 amplified (FISH+)
HER2 Structure

Domain I
Domain II
Domain III
Domain IV

Extracellular domain

Transmembrane domain

Intracellular domain

Trastuzumab (bound)

Tyrosine kinase domain

Lapatinib binding site

Park et al. Clin Breast Cancer 2008; adapted with permission from Leahy et al. Cancer Cell
HER2 Signaling Pathways

Park et al., Clin. Breast Cancer 2008
“LIQUID BIOPSY”

CTC Analysis

- Detection / Enumeration
- Transcriptome via expression array
- Copy number via CGH
- Mutation analysis
- Whole genome via NGS

FISH analysis of IE/FACS-isolated BT474

Isolated Tumor Cells

Normal Leukocyte Control

CEP17       HER2       Merged w/ DAPI
SERIAL ANALYSIS OF CTCs & MATCHED PRIMARY TUMOR

Patient #4013
50 yo F
ERpos HER2pos M

Day 15 (20 CTCs)
8.5 CTC/ml

Day 56 (20 CTCs)
40.5 CTC/ml

Primary tumor
6 yrs earlier
LIPIDIC NANOPARTICLES
From Liposomes to Novel Multifunctional Constructs

• Liposomes as scaffold
  • Biodegradable, safe, manufacturable
  • “Stealth” = non-immunogenic, long circulating
  • Clinically validated system with multiple agents in use

• Limitations of previous liposomes
  • Efficient drug loading has historically been limited
    (anthracyclines, amphotericin)
  • No direct tumor cell targeting

• Next Generation Lipidic Nanoparticles
  • Increased versatility of delivery
  • Molecular targeting (e.g. MAb)
  • Multicapability systems approach incl. imaging

J Park, Nanotechnology in Oncology, ASCO 2006
IMMUNOLIPOSOMES (ILs): Targeted Drug Delivery

**Tumor Cell Targeting**
- Binding
- Internalization

**Drug Delivery**
- High capacity carrier
- Repertoire of drugs
  - Approved chemoRx
  - Novel compounds
- Long circulation as stable construct
- Non-immunogenic
- Bystander killing
HER2-Targeted ILs-Dox: Superior to Combinations

vs. Free Dox + Trastuzumab

vs. Doxil + Trastuzumab

Park et al., Clin. Cancer Res. 2002
HER2-Targeted ILs-Dox  
*Translation to the Clinic*

- **NSC 701315**
  - GMP scale up and manufacturing by NCI DTP (DDG/RAID)

- **AP49**
  - Licensed to ALZA/Johnson&Johnson
  - Primate tox completed:
    - Cardiotoxicity: ILs = PLD/Doxil << Free Doxorubicin
    - HER2 undetectable in primate myocardium at necropsy
  - GMP manufacturing at ALZA/Centocor
  - ALZA closed by Johnson&Johnson

- **MM302**
  - Licensed to Merrimack Pharmaceuticals
  - PreIND meeting completed
  - GMP manufacturing at Merrimack
  - IND filing Jan 2011
HER2-Targeted ILs-Dox: 
Current Registration Trial

Herceptin

Current Registration Trial

NSC701315 / MM-302

HERMIONE Trial

- Arm A (Experimental Arm)
  - 6 mg/kg trastuzumab*, Q3W
  - 30 mg/m² MM-302, Q3W
- Arm B (Control Arm)
  - 6 mg/kg trastuzumab*, Q3W
  - Chemotherapy of Physician’s Choice (capecitabine, gemcitabine or vinorelbine)

250 patients → randomized 1:1

The study will occur in approximately 60 sites

North America (~40)
- Canada
- United States

Western Europe (~20)
- Austria
- Italy
- Spain

- Belgium
- France

NanoLiposomal Irinotecan/CPT-11

- “Nano-X” encapsulation
  ~100% efficiency
  10^5 drugs/particle
- Drug stability
  >90% drug retention in circulation (released drug undetectable)
- PK
  Long circulating

Drummond et al., Cancer Res. 2006
Noble et al., Cancer Res. 2006
NanoLiposomal CPT-11
Clinical Development

• “PEP02”
  – Partnership with PharmaEngine (Taiwan)
  – GMP manufacturing, toxicology -> clinic

• FIH Phase I Trial
  – Taipei: CGMH, NHRI, NTUH
  – Responses observed

• Phase II Trials
  – Phase II in Pancreas (UCSF, A Ko): increased OS vs. historic
  – Other tumor types

• Phase III in Pancreas (NAPOLI-1, Merrimack Pharma)
  – NanoLiposomal CPT-11 + 5FU/LV vs. 5FU/LV showed superior OS

• “OnivydeTM” (Irinotecan Liposome Injection)
  – US FDA approval 2015
  – NCCN Guideline listed
Median OS
HR=0.68 [95% CI: 0.50, 0.93]; log-rank p=0.014

- ONIVYDE + 5-FU/LV (95% CI: 4.8, 8.5) 6.1 MONTHS
- 5-FU/LV (95% CI: 3.3, 5.3) 4.2 MONTHS

# at risk:
ONIVYDE + 5-FU/LV: 117 99 51 20 8 0 0
5-FU/LV: 119 73 37 12 7 1 12

1-year probability of survival was
24% with ONIVYDE + 5-FU/LV and 17% with 5-FU/LV alone

Wang-Gilliam et al., Lancet 2015
SUMMARY

- **Diagnosis -> Biomarker defined**
  - Recent example: HER2+ Breast Cancer
  - Current example: Liquid biopsy

- **Therapy -> Targeted**
  - Recent example: Trastuzumab (Herceptin™)
  - Current example: Nanoparticle drugs

- **Impact -> Translational**
  - Bench to Bedside / Clinic
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