Clinical Trials and Personalized Medicine

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Outline

• Clinical trials
• Primer on basic cell biology and how that ties to cancer development
• *Personalized Medicine* and genetic testing
• Connecting patients to trials
Clinical Trials

- We need new therapies for chordoma
- Clinical trials are how we test new ways to treat chordoma
Drug Development and Clinical Trials
Drug Development and Clinical Trials

Phase I

Is it safe? What dose?
Standard Phase I “3+3” Design

Modified from Hansen et al 2014, LeTourneau 2009
Drug Development and Clinical Trials

Phase I
Is it safe? What dose?

Phase II

Any sign of activity?
New Drug A

Fixed number of patients (e.g. 30) with same type of cancer
Everyone gets the same dose and drug
No placebo
Looking to show drug is better than expected in what is typically seen in other patients
Drug Development and Clinical Trials

Phase I
- Is it safe? What dose?

Phase II
- Is it better?

Phase III

Any sign of activity?
New Drug A compared to a standard therapy or placebo
Drug Development and Clinical Trials

Discovery

Phase I

Phase II

Phase III

Time/Money: 10+ years
$1 billion
Drug Development and Clinical Trials

In all cancers – need to be smarter about matching patients to trials
Need to move on early if not showing a meaningful effect

Unique challenges for rare tumors
Basic cancer cell biology

PERSONALIZED MEDICINE
How does cancer develop?

30 thousand genes
30 trillion cells in the body
70 billion cell divisions per day
10 thousand to 1 million mistakes/injuries per cell per day
How does cancer develop?

- Resist cell programmed death
- Genome instability
- Activate invasion programs
- Uncontrolled growth
- Avoid immune surveillance
- Angiogenesis (blood vessel growth)
How we think about new ways to kill cancer cells:

- New Chemo
- Delivery Techniques
- Resist cell programmed death
- Uncontrolled growth
- Avoid immune surveillance
- Mutation-targeted therapies
- Immunotherapy
- Genome instability
- Activate invasion programs
- Angiogenesis (blood vessel growth)
- DNA repair inhibitors
- Angiogenesis Inhibitors
Genetic Testing Logistics
Genetic Testing Logistics

Commercial Testing

In general they cover a subset of known cancer genes
Vary in number of genes, ‘hot spots,’ clinical reporting, cost

Academic Testing

Many hospitals have their own:
MGH, DFCI, JH, MSKCC, etc
Built in to the NCI-Match trial

In general they cover a subset of known cancer genes
Vary in number of genes, ‘hot spots,’ clinical reporting, cost
Genetic Testing

| ABL1 | C11560 EMMP | GCR2 | FGFR4 | ELF4 | MET | PHKCA | SQK40 | TGK31 |
| ABL2 | C02015 DDCS | FGFR4 | PHE | HHB4 | hMTF | PHG4B | S7E02 | LGH31 |
| ACVR1B | CBPS | DNMT3A | FLN4 | HNRPB | MLH1 | PHG20 | SF3B1 | VEGF4 |
| AKT1 | C2L1 | DOPL1 | FML1 | HNP2 | MNK | SCH1 | S7E21 | VHL |
| AKT2 | C2N014 EKFR | FTV3 | HNF4 | ME3A | MIR292 | SH2D2 | WIF1 |
| AKT3 | C2N012 | EP300 | FLK4 | JN22 | MIR | MS44 | SMAD2 | WT1 |
| ALK | C2N013 | EMER | FOSL2 | JAK1 | MSF2 | PHD2 | SMAD4 | XPO1 |
| AKIR | C2N015 | EPSS3 | FOSL2 | JAK1 | MSF2 | PHD2 | SMAD4 | XPO1 |
| ARL1 | C2N018 | ERBB3 | FOSL2 | JAK2 | MYD11 | MPED | TAP1 | ZEB12 |
| ARK | C2P177 | ERBB4 | FOSL2 | JAK2 | MYD11 | MPED | TAP1 | ZNF103 |
| ARF | C2P179 | ERBB4 | FOSL2 | JAK2 | MYD11 | MPED | TAP1 | ZNF103 |
| ARAF | C2P179 | ERBB4 | FOSL2 | JAK2 | MYD11 | MPED | TAP1 | ZNF103 |
| ARAF | C2P179 | ERBB4 | FOSL2 | JAK2 | MYD11 | MPED | TAP1 | ZNF103 |
| ARAF | C2P179 | ERBB4 | FOSL2 | JAK2 | MYD11 | MPED | TAP1 | ZNF103 |
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| ARAF | C2P179 | ERBB4 | FOSL2 | JAK2 | MYD11 | MPED | TAP1 | ZNF103 |

SELECT REARRANGEMENTS

| ALK | EML4 | ERBB2 | ETV1 | ETV4 | ETF5 | KIT | MIC | NTRK1 | ROS1 | RET |
| BCR | BCR2 | ETV3 | ETV4 | GEPX | MIR3 | PAF1 | ROR1 | RET | RET |

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER
Genetic Testing Logistics

• *Should be only be sent when ready for a clinical trial*
Genetic Testing Logistics

- Many limitations:
  - High cost
  - Unlikely coverage by insurance (issues in particular with Medicaid)
  - Technology is evolving rapidly
  - Utility in chordoma remains unknown

- **Do not pay for this yourself**
Which trial is right for me?

- Chordoma subtype
- Chordoma rate of growth
- Prior therapies
- Visit schedule / distance traveled
- Other medical problems
- Insurance
Which trial is right for me?

Chordoma subtype specific

Conventional

Poorly Differentiated

1. ?Appropriate chemo given
2. Tazemetostat
Which trial is right for me?

Conventional

1. Open chordoma-specific trials:
   • Localized, RT candidate → vax/RT
   • Proton pencil beam study (?closed)
   • Nilotinib/RT (closed)
2. Genetic targets → Phase 1 (or 2) or basket
3. Novel Phase 1 Agents
4. Off-label
Finding new therapies for chordoma
THANK YOU