ORGANIZATION AND ROLE OF A PHASE I ONCOLOGY UNIT

Dr Philippe CASSIER
Centre Léon Bérard, Lyon
Outline

- Cancer & Oncology
- Drug development in oncology
- Specificity of phase I trials in oncology
- Study design
- Practical aspects of phase I trials
Cancer

- Approximately 1.5 Million new cases per year in the US and 1.7 Million new cases in Europe
- Over 550,000 deaths per year in the US and 956,000 in Europe
- Second cause of death in the US, leading cause of death in France

Sources
Cancer & oncology
Cancer

Carcinoma
Reactive tumour stroma

VEGF receptor
Protease
ECM fragment
Risk of developing an invasive cancer by age group
# Cancer Epidemiology

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>192,280</td>
<td>192,370</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,090</td>
<td>103,350</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>75,590</td>
<td>71,380</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>52,810</td>
<td>42,160</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>39,080</td>
<td>29,990</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>35,990</td>
<td>29,640</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>35,430</td>
<td>27,200</td>
</tr>
<tr>
<td>Leukemia</td>
<td>25,630</td>
<td>22,330</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>25,240</td>
<td>21,550</td>
</tr>
<tr>
<td>Pancreas</td>
<td>21,050</td>
<td>21,420</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>766,130</strong></td>
<td><strong>713,220</strong></td>
</tr>
</tbody>
</table>

*Estimated New Cases*
Basics of cancer therapy

- Surgery is the mainstay of curative therapy for most (but not for all) cancers
- Radiation may be used as adjunct to surgery or as the sole modality of local therapy
- Medical treatments (i.e. chemotherapy)
  - Peri-operative
  - Palliative (advanced disease)
  - Curative in some disease (lymphoma, leukemia, germ cell tumors)
Systemic therapy

- Peri-operative:
  - Reduce tumor load with the aim of reducing surgical morbidity
  - Reduce recurrence rate/improve cure rates
  - Delay recurrence (if inevitable)

- Advanced disease
  - Aliviate cancer-related symptoms → improve quality of life
  - Prolong survival
Drug development in oncology
Drug development in oncology

- Overall very complex because of the complexity and heterogeneity of the diseases
- High attrition rates increases costs

Kola & Landis Nat Rev Drug Discov 2004
Drug development in oncology

Changes in reasons for attrition over time

Kola & Landis Nat Rev Drug Discov 2004
Classic drug development

N=0

Drug discovery (more or less fortuitous, animal toxicology)

Pre-clinical
Classic drug development

Pre-clinical

Drug discovery (more or less fortuitous, animal toxicology)

N=0

Clinical safety, recommended phase 2 dose (RP2D)

N=20-30

Phase 1
Classic drug development

- **Pre-clinical**
  - Drug discovery (more or less fortuitous, animal toxicology)

- **Phase 1**
  - Clinical safety, recommended phase 2 dose (RP2D)

- **Phase 2**
  - Efficacy, safety in a specific patient population

- **N=0**
  - Drug discovery

- **N=20-30**
  - Clinical safety, recommended phase 2 dose (RP2D)

- **N=30-50**
  - Efficacy, safety in a specific patient population
Classic drug development

- **Pre-clinical**
  - N=0
  - Drug discovery (more or less fortuitous, animal toxicology)

- **Phase 1**
  - N=20-30
  - Clinical safety, recommended phase 2 dose (RP2D)

- **Phase 2**
  - N=30-50
  - Efficacy, safety in a specific patient population

- **Phase 3**
  - N=500-5000
  - Randomized comparison to standard of care in a given population

- **N=0**
- **N=20-30**
- **N=30-50**
- **N=500-5000**
Classic drug development

Pre-clinical

- Drug discovery (more or less fortuitous, animal toxicology)

Phase 1

- Clinical safety, recommended phase 2 dose (RP2D)

Phase 2

- Efficacy, safety in a specific patient population

Phase 3

- Randomized comparison to standard of care in a given population

Registration

N=0

N=20-30

N=30-50

N=500-5000

N=0
Classic drug development

- Pre-clinical: Drug discovery (more or less fortuitous, animal toxicology)
- Phase 1: Clinical safety, recommended phase 2 dose (RP2D)
- Phase 2: Efficacy, safety in a specific patient population
- Phase 3: Randomized comparison to standard of care in a given population
- Phase 4: More safety, long term follow up.
How has this changed in recent years?

**Improved**

- understanding of cancer biology
- understanding in physiology
- biotechnology
  - Protein synthesis
  - Sequencing and other nucleic acid technology
- Models (PK, PD, ....)

TARGETED THERAPIES FOR THE TREATMENT OF CANCER
Schéma moderne

Possible target

Target identification

Pre-clinical

Drug discovery (more or less fortuitous, animal toxicology)

Phase 1

Clinical safety, recommended phase 2 dose (RP2D)

Phase 2

Efficacy, safety in a specific patient population

Phase 3

Randomized comparison to standard of care in a given population

Phase 4

More safety, long term follow up.

N=0

N=20-30

N=30-50

N=500-5000

Registration
Schéma moderne

Possible target

Exploratory phase
Pre-clinical → Clinical

Validation phase
- Preclinical
- Clinical
- Biomarker identification

Target identification

Drug discovery (more or less fortuitous, animal toxicology)
Clinical safety, recommended phase 2 dose (RP2D)
Efficacy, safety in a specific patient population
Randomized comparison to standard of care in a given population

N=0
N=20-30
N=30-50
N=500-5000

Phase 1
Phase 2
Phase 3
Phase 4

REGISTRATION

More safety, long term follow up.

N=0
N=20-30
N=30-50
N=500-5000

Randomized comparison to standard of care in a given population

Pre-clinical
Phase 1
Phase 2
Phase 3
Phase 4

Drug discovery (more or less fortuitous, animal toxicology)
Clinical safety, recommended phase 2 dose (RP2D)
Efficacy, safety in a specific patient population
Randomized comparison to standard of care in a given population

N=0
N=20-30
N=30-50
N=500-5000

Drug discovery (more or less fortuitous, animal toxicology)
Clinical safety, recommended phase 2 dose (RP2D)
Efficacy, safety in a specific patient population
Randomized comparison to standard of care in a given population

N=0
N=20-30
N=30-50
N=500-5000

Drug discovery (more or less fortuitous, animal toxicology)
Clinical safety, recommended phase 2 dose (RP2D)
Efficacy, safety in a specific patient population
Randomized comparison to standard of care in a given population

N=0
N=20-30
N=30-50
N=500-5000

More safety, long term follow up.
Schéma moderne

**Pre-clinical**
- Drug discovery (more or less fortuitous, animal toxicology)

**Phase 1**
- Clinical safety, recommended phase 2 dose (RP2D)

**Phase 2**
- Efficacy, safety in a specific patient population

**Phase 3**
- Randomized comparison to standard of care in a given population

**Phase 4**
- More safety, long term follow up.

- **Possible target**
  - Target identification

- **Exploratory phase**
  - Pre-clinical \(\rightarrow\) Clinical

- **Validation phase**
  - Preclinical
  - Clinical
  - Biomarker identification

PoC
Schéma moderne

Pre-clinical

Possible target

Exploratory phase
Pre-clinical ➔ Clinical

Target identification

Validation phase
- Preclinical
- Clinical
- Biomarker identification

PoC

Confirmation phase

Randomized trial on a small cohort of selected patient

Phase 1

Clinical safety, recommended phase 2 dose (RP2D)

Phase 2

Efficacy, safety in a specific patient population

Phase 3

Randomized comparison to standard of care in a given population

Phase 4

More safety, long term follow up.

Drug discovery (more or less fortuitous, animal toxicology)

Drug discovery

N=0

N=20-30

N=30-50

N=500-5000

Drug discovery

Randomized trial on a small cohort of selected patient

Randomized comparison to standard of care in a given population

Efficacy, safety in a specific patient population

Clinical safety, recommended phase 2 dose (RP2D)

Clinical safety, recommended phase 2 dose (RP2D)

Pre-clinical

Phase 1

Phase 2

Phase 3

Phase 4

Phase 4
Phase 1 trials

- Specificity in oncology: these trials enroll patients (as opposed to volunteers)
- Strong academic-pharmaceutical collaboration

Aims/goals
- Identification of the maximum tolerated dose and establish the recommended phase 2 dose
- Describe the safety profile
- Describe preliminary pharmacokinetics
Phase 1 trials

- Aim 1: define the correct dose and schedule for further development: Recommended Phase II Dose (RP2D) based on:
  - Safety
  - Pharmacokinetics (PK) / pharmacodynamics (PD)
  - Activity
Safety

- A major issue with all drug therapies.
- Given the sample size, phase 1 trials can only detect very frequent side effects.
- To define the MTD you need to define the dose limiting toxicities (DLT).
Phase 1 trials

- Aim 1: define the correct dose and schedule for further development: Recommended Phase II Dose (RP2D) based on:
  - Safety
  - Pharmacokinetics (PK) / pharmacodynamics (PD)
Pharmacokinetics: the study of the mechanisms of absorption and distribution of an administered drug, the chemical changes of the substance in the body and the effects and routes of excretion of the metabolites of the drug.

"It’s what your body does to the drug"
Definition

- **Pharmacodynamics**: the study of the biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect.

  ➔ “it’s what the drug does to your body”
Phase 1 trials

Aim 1: define the correct dose and schedule for further development: Recommended Phase II Dose (RP2D) based on:

- Safety
- Pharmacokinetics (PK) /pharmacodynamics (PD)
- Activity
Phase 1 trials

- As with all things in science (in life?) the answer you get is closely linked to the way you asked the question....
Study design
Study design(s)

- Phase I studies are (in general) dose-escalation studies.
- Dose-escalation is (in general) inter-patient (as opposed to intra-patient)
- Several statistical models can be used to guide dose-escalation
  - Standard 3+3
  - Bayesian model (CRM, EWOC....)
Different designs have different advantages

- 3+3 is easy
- CRM and EWOC require a little bit more patients but are more accurate and you need a statistician
- Some designs can be combined

Example of Bayesian design

- Pre-clinical information, evidence of the trial data, statistical modeling and overdose control criteria principle support escalation of XXX dose up to 600 mg
  → Predicted chance of overdose given observed data = 23.2%

- XXX dose which maximizes the probability to be in the target toxicity is 460 mg (recommended)
  → Predicted chance of overdose given observed data = 13.7%

- If treatment-related toxicities of CTCAE grade 2 are observed in at least 2 patients or if any patient experiences a grade 3 or higher treatment-related toxicity at the current dose level, then the maximum dose is 520 mg (risk of overdosing 14.7%)
Dose escalation for combinations

Selecting the starting dose

**Toxicology**
- Determine the No observable Adverse Effect Level (NOAEL)
- Convert NOAEL to Human Equivalent Dose (HED)
  - adjust for anticipated exposure in man
  - adjust for inter-species differences in affinity / potency
- Apply a $\geq 10$ fold safety factor

**Pharmacology**
- Estimate the Minimal Anticipate Effect Level (MABEL)
  - justify based on pharmacology
  - adjust for anticipated exposure in man
  - include anticipated duration of effect
  - adjust for inter-species differences in affinity / potency

---

**“Maximum Recommended Starting Dose”**
- define anticipated safety window based on NOAEL and MABEL
- appropriate safety factor, if necessary, based on potential risk
Biomarkers

- Biomarkers are key in the development of targeted therapies
- How do you integrate biomarker studies into early clinical trials?
  - Blood born markers (proteins, PBMC, nucleic acids)
  - Tumor tissue
  - Surrogate markers.
General inclusion criteria

- Sick patients that aren’t (to) sick….
  - PS 0-1 (ECOG ou OMS)
  - Adequate cardiac, renal and liver function
  - Adequate bone marrow function
  - Should have exhausted standard therapeutic options
  - In FITH: any histology
Practical aspects
Resources

- The team:
  - Doctors
  - Clinical trial nurses
  - Clinical trial organisers/clinical research assistant
  - Data managers

- Every one needs to be GCP trained
Resources

- In patient beds, day hospital beds, clinic rooms
- Freezers, refrigerators, centrifuges
- Radiology department
- ICU (ideally)
- PET-scan
Operation

- Ideally 24/7
- But not really feasible
- Cannot be a part time activity
- Most visits and tests cannot be outsourced
### Study Flowchart

<table>
<thead>
<tr>
<th>Assessment Window (days)</th>
<th>Screening&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cycle 1</th>
<th>Cycles ≥2</th>
<th>Cycles 2, 4, 6, 8, 12, and 16</th>
<th>Study Completion or Early Termination&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days -28 to −1</td>
<td>Days -28 to −1</td>
<td>1</td>
<td>2</td>
<td>4 or 5</td>
<td>8 (±1)</td>
</tr>
<tr>
<td>Review of eligibility criteria</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical, surgical, and cancer histories, including demographic information&lt;sup&gt;2&lt;/sup&gt;</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV serology</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medications&lt;sup&gt;4&lt;/sup&gt;</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor assessment&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA-125 or PSA assessment&lt;sup&gt;9&lt;/sup&gt;</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete physical examination&lt;sup&gt;7&lt;/sup&gt;</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited physical examination</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-lead electrocardiogram&lt;sup&gt;4&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local laboratory assessments</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum chemistry&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulation panel (aPTT, INR)</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td>x&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Administrative aspects

- Lots of paperwork
- Lots of teleconferences
Why do we do it?
It’s strategic

- Gives you a glimpse of what tomorrows medicine is going to be.
- When the time comes to do phase II trials, you are the first person the Pharmaceutical industry is going to talk to.
- And as institutions, the more trials, the more options you have, the more attractive you are...
Thanks! Questions?