Drug Development and Clinical Trials

MBChB221B Clinical Pharmacology and Therapeutics
Lecture
2019

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Slide 2

Agenda
❑ Understanding Drug Development
❑ Biomarkers
❑ Purpose of Clinical Trials
❑ Clinical Trial Designs
❑ Drug Development Case Studies

Slide 3

Learning Objectives
❑ Understand the drug development process
❑ Appreciate the regulatory environment for bringing a therapeutic drug from bench to bedside
❑ Distinguish preclinical and clinical development processes
❑ Awareness of the time, cost and attrition challenges
❑ Learn about the design and conduct of clinical trials
❑ Learn about the development of some therapeutic drugs
Agenda

- Understanding Drug Development
- Biomarkers
- Purpose of Clinical Trials
- Clinical Trial Designs
- Drug Development Case Studies

Classes of Therapeutic Agents

- Pharmaceutical Drugs
- Gene Therapies
- Cell Therapies

**Small Molecules**
- Low molecular weight (typically < 500 Da)
- Chemically synthesized
- Able to enter cells easily
- Most approved drugs fall into this class

**Large Molecules**
- High molecular weights
- Made by assembly of smaller monomer units
- May need ‘protection’ to prevent degradation or help to enter a cell (delivery system) depending on site of action and chemical properties (size, charge, lipophilicity)

Large molecules are high molecular weights, made by assembly of smaller monomer units and may need 'protection' to prevent degradation or assistance to enter a cell if their site of action is intracellular and depending on chemical properties. Delivery systems may use nanoparticles to encapsulate a drug or conjugation to a ligand, both of which will alter the pharmacokinetic properties of the drug.
There is a wide diversity of molecules that are larger than small molecules (typically less than 500kDa) consisting of nucleic acids, proteins and ligand-drug conjugates.

Oligonucleotide are short strands of DNA or RNA that have different mechanisms of action.

- Antisense oligos are short strands of DNA/RNA that regulate mRNA function and hence protein expression through either a RNaseH-dependent degradation mechanism (gapmers) or by blocking regulatory binding sites (mixmers). There are several currently approved, including Kynamro for homozygous familial hypercholesterolemia, Eteplerin for muscular dystrophy and Nusinersin for spinal muscular atrophy.

- siRNA silence mRNA expression through an RNA-induced-silencing complex (RISC) mechanism. The first therapeutic in this class has just been approved (Patisiran).

- Aptamers are short oligos that bind and modulate protein function. Eg. Macugen is an anti-angiogenic for age-related macular degeneration.

A new emerging class of RNA therapeutics are mRNA that are being developed as replacement therapies and vaccines.

Protein based drugs are made of amino acids and consist of peptides, antibodies or proteins such as enzymes.

Ligand-drug conjugates are used as targeted delivery systems for either small molecules, ASO or siRNA and will be discussed in more detail in one of the next slides.

As the size of these agents increases so does their complexity.
Increasing Size & Complexity

Different Ways Drugs Are Made

- Oligonucleotides
- Peptides
- Antibodies
- Small molecules
- Chemical Synthesis (chemical entities)
- In Vitro Transcription (IVT)
- Living Cells (biologics)
- mRNA
- Antibodies
- Other proteins

The drugs are made in different ways using chemical synthesis or by harnessing a cell's ability to make proteins (biologics). The new class of mRNA therapeutics is made by in vitro transcription and is considered a new class of biologics.

Delivery Systems That Help Protect And Target

- GalNac (N-acetylgalactosamine) is a sugar ligand for the asialoglycoprotein receptor and is being investigated for delivery of siRNA and ASO.
Drug discovery and development is a staged process aligned within a regulated environment that is also staged. The activities within this process are not linear, often occurring in a reiterative and parallel fashion.

Drug discovery processes are not as highly regulated as those that occur during drug development, though good practices still apply. The documentation requirements are not as onerous. Why? Because there is a lot of screening and optimization occurring with many drugs discarded because they do not meet defined efficacy, pharmacokinetic, metabolism or safety thresholds. This process is reiterative and many assays are run in parallel until a candidate drug is identified.

The key regulatory milestones occur prior to conducting clinical trials and approval to market. These are the Investigation New Drug (IND) application and the New Drug Approval (NDA) in the USA.

Question

- Why Is the Regulatory Process Staged?
The Regulatory Process Is Staged To Ensure….

- **Good quality & safe products** with potential to improve human health are progressed into the clinic
- **Safety risks** are minimized by conducting studies according to regulatory standards
  - Preclinical testing before first time in humans
  - Staged clinical trials before approval to market
- **Governance** of sale, marketing & manufacturing practices post-market approval
- **Post-market monitoring** occurs (pharmacovigilence)

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Drug Discovery

A preclinical research process that identifies new candidate drugs

- Identify the drug target and initiate validation
- Screen and identify leads
- Optimize leads
- Select a candidate drug that meets defined criteria

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Preclinical Development

A phase of drug development where preclinical studies are completed to support the first critical regulatory submission for approval to conduct clinical trials of an Investigational New Drug (IND).

Drug must meet regulatory standards:

- **Pharmacology & Drug Disposition**
  - Pharmacological effects & mechanism of action
  - Absorption, distribution, metabolism & excretion (ADME), Pharmacokinetics (PK)
- **Safety (GLP)**
  - Toxicology
  - Safety pharmacology
- **Chemistry, Manufacturing & Controls (cGMP)**
- **Clinical Protocol & Investigators (cGCP)**

GLP = Good Laboratory Practices
cGMP = current Good Manufacturing Practices
cGCP = current Good Clinical Practices
Role Of Preclinical Pharmacology Studies

- Demonstrates efficacy-exposure relationships and mechanism in appropriate preclinical models
  - Examines efficacy, pharmacodynamic (PD) & PK relationships
- Understand absorption, distribution, metabolism & excretion profile (ADME)
- Informs risk assessment for achieving a predicted efficacious dose in humans
- Supports the proposed clinical investigations:
  - Demonstrates efficacy and mechanism in models representing features of the disease or intended patient population
  - Defines efficacy/PD, PK & time relationships that help guide
  - Route of administration
  - Dose
  - Dosing schedule
  - Biomarkers
  - Drug combinations

Role Of Preclinical Safety Assessments

Determine whether the drug is probably safe to administer to humans and demonstrates an acceptable safety margin (based on animal studies)

- Rules-out drugs with specific toxicity risks using in vitro assays
- Scope of animal studies depends on the duration and nature of the proposed clinical investigations:
  - Acute and chronic repeat dose studies in 2 animal species
  - Identify toxicities and assess risks
  - Define toxicity-exposure relationships
  - Determine if there is an acceptable safety margin above the human dose
  ✓ Based on reaching maximum tolerated or feasible dose (MTD/MFD) and no-observed-adverse-effect level (NOAEL)
  ✓ A suitable safety factor is applied to NOAEL to guide the first in human dose

Chemistry, Manufacturing & Controls (CMC)

- CMC must comply with set standards known as ‘current Good Manufacturing Practices’ (cGMP)
- Some of the processes include:
  - Optimization of route of synthesis for scale-up
  - Stability of drug product
  - Characterization of drug product
  - Control of drug product, any excipients & formulation
  - Control of manufacturing process, labelling, packaging, storage & transportation conditions

Examples of toxicity risks that are assessed using in vitro assays:

- No unreasonable interactions with other drugs
- No risk of genotoxicity such as mutagenesis and chromosome aberrations
- No risk of cardiotoxicity from QT interval prolongation (an electrical wave measurement)

Determine from animal safety studies whether the drug has any unwanted risk of liver, heart, respiratory system or CNS toxicity
Clinical Protocol & Investigators

- Clinical protocol describes the clinical trial design and how the clinical trials are to be conducted
  - Patients, drug administration, dosing schedule, sample collection schedule, monitoring, etc.
  - Investigators
  - Patient consent & privacy
- Must comply with set standards known as “current Good Clinical Practices” (cGMP)

Current Good Clinical Practice (cGCP)

- Clinical Study requirements are governed by cGCP
- GCP is a collection of directives, regulations, guidelines and SOP’s defining responsibilities of sponsor and investigator
- Purpose of GCP is to protect the study subjects rights and safety
- Some of the processes include:
  - All clinical trial information should be recorded, handled and stored allowing accurate reporting, interpretation and verification.
  - Confidentiality
  - Investigational products to be manufactured, handled and stored in accordance with GMP and used in accordance with the approved protocol.
  - SOP’s that assure the quality of every aspect of the trial should be implemented.
  - Responsibilities of Ethics Committee, Investigator and Sponsor are defined

Responsibilities of Sponsor

Industry-sponsored trial: Sponsor is Pharmaceutical, Biotech or Medical Device company
Investigator-initiated trial (or investigator-sponsored trial): Sponsor is a qualified Investigator

- Overall responsibility for the Study
- Multiple responsibilities to participants, investigators, authorities & within the company
- Responsibilities include:
  - Defining responsibilities
  - Can delegate some responsibilities to a CRO (in writing)
  - Supplying quality systems with standard operating procedures
  - Providing medical expertise (answering questions)
  - Trial design, management, data handling, statistics, report writing & record keeping
  - Many other responsibilities (refer to notes)

Sponsor has overall responsibility for the Study which includes:

- Quality systems with written Standard Operating Procedures (SOP’s)
- Can delegate responsibilities to a CRO – in writing
- Provision of medical expertise – answering questions
- Trial design, management, data handling, statistics, reports writing and record keeping
- Investigator selection and written agreement – based on GCP experience, workload, recruitment potential, staffing, facilities etc
- Allocation of duties and functions using
<table>
<thead>
<tr>
<th>Responsibilities of Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>An Investigator is a physician qualified by education, training and experience familiar with the use of the investigational product described in the protocol.</td>
</tr>
</tbody>
</table>

- Overall responsibility to ensure proper conduct of the trial and medical care of participants at their site
- Responsibilities include:
  - Complies with GCP & applicable regulatory and protocol requirements
  - Permits monitoring, auditing and inspection
  - Maintains a list of persons with delegated responsibilities
  - Has adequate resources (subjects, time, staff, facilities)
  - Ensures all persons involved at site are adequately informed
  - Responsible for medical care and trial-related decisions
  - Obtain informed consent (signed and dated)
  - Report Serious Adverse Events immediately
  - Many other responsibilities (refer to notes)

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- Investigator responsibilities include:
  - Comply with GCP and applicable regulatory and protocol requirements
  - Clinical Trial Agreement
  - Permit monitoring, auditing and inspection
  - Maintain a list of persons with delegated responsibilities
  - Needs to have adequate resources (subjects, time, staff, facilities)
  - Ensure all persons involved at site are adequately informed
  - Responsible for medical care and trial-related decisions
  - Inform subjects primary physician
  - Communication with Ethics including obtaining written approval for the study and any updates
  - Responsible for investigational non-compliance
  - Premature termination or suspension of a study
  - Provision of Clinical Trial Reports
  - Ensure participant confidentiality
  - Retain essential documents (10 years) after completion

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  - Report Serious Adverse Events immediately
  - Many other responsibilities (refer to notes)
product accountability
- Obtain informed consent (signed and dated)
- Ensure the accuracy, completeness, legibility and timeliness of data in the Case Report Forms
- Maintain trial documents including archiving of study records
- Report Serious Adverse Events immediately

It's A Long, Costly & Risky Road
The process of bringing a drug from idea stage to market
- Can take approximately 15 years
- Cost is approaching $3B*
- Has high attrition rates

Causes Of High Attrition Rates
- Poor pharmacokinetics
- Lack of efficacy
- Safety issues
- Commercial interests
- Market competition
- Patent protection expiry
Clinical Trial Attritions

- Only 10-15% of drugs tested in humans are approved
- Failure usually due to poor pharmacokinetics, safety issues or unable to meet primary endpoint
- Success rate is lowest in Phase 2
  - Larger number of patients than Phase 1
  - Evaluating both safety & efficacy in disease setting

A Drug Discovery & Development Productivity Model

Predicts that at least 9 molecular entities need to enter clinical development to yield 1 new molecular entity launch (every year)

Model based on industry performance assumptions
Calculates the number of assets (work in progress, WIP) to achieve one new molecular entity launch

Top Therapeutic Drugs & Companies

### Top Selling Therapeutic Drugs in 2018

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Drug</th>
<th>Type</th>
<th>Mechanism</th>
<th>Main Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humira</td>
<td>Adalimumab</td>
<td>Biologic</td>
<td>Anti-TNFα mAb</td>
<td>Immunology</td>
</tr>
<tr>
<td>Revlimid</td>
<td>Lenalidomide</td>
<td>Small molecule</td>
<td>Multiple</td>
<td>Cancer</td>
</tr>
<tr>
<td>Keytruda</td>
<td>Pembrolizumab</td>
<td>Biologic</td>
<td>Anti-PD1 mAb</td>
<td>Cancer</td>
</tr>
<tr>
<td>Herceptin</td>
<td>Trastuzumab</td>
<td>Biologic</td>
<td>Anti-HER2 mAb</td>
<td>Cancer</td>
</tr>
<tr>
<td>Avastin</td>
<td>Bevacizumab</td>
<td>Biologic</td>
<td>Anti-VEGF-A mAb</td>
<td>Cancer</td>
</tr>
<tr>
<td>Rituxan</td>
<td>Rituximab</td>
<td>Biologic</td>
<td>Anti-CD20 mAb</td>
<td>Cancer</td>
</tr>
<tr>
<td>Opdivo</td>
<td>Nivolumab</td>
<td>Biologic</td>
<td>Anti-PD1 mAb</td>
<td>Cancer</td>
</tr>
<tr>
<td>Eliquis</td>
<td>Apixaban</td>
<td>Small molecule</td>
<td>Factor Xa inhibitor</td>
<td>Vascular injury</td>
</tr>
<tr>
<td>Prevnar</td>
<td>Pneumococcal 7-valent Conjugate Vaccine</td>
<td>Vaccine</td>
<td>Immunization against S. pneumonia subtypes</td>
<td>Paediatric Immunization</td>
</tr>
<tr>
<td>Stelara</td>
<td>Ustekinumab</td>
<td>Biologic</td>
<td>Anti-IL12 &amp; IL23 mAb</td>
<td>Immunology</td>
</tr>
</tbody>
</table>

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### Agenda

- Understanding Drug Development
- Biomarkers
- Purpose of Clinical Trials
- Clinical Trial Designs
- Drug Development Case Studies
Biomarkers and Outcomes

- **Biomarker**
  Readily measurable marker of response

- **Surrogate**
  A biomarker substitute for a clinical endpoint as although there maybe an association the relationship is not guaranteed

- **Clinical Endpoint/Outcome**
  How the patient functions/feels/survives
  Evaluates patient benefit

Pharmacodynamic Biomarkers

- A measurable molecular or biological response caused by the drug

- May be the drug target itself, an associated downstream component of the signaling pathway or cellular consequence

- Measurable in an accessible disease tissue or a surrogate tissue

- Used to understand if sufficient drug exposure has been achieved to modulate the drug target

- Helps early stage clinical trials identify doses and a dosing schedule to evaluate efficacy

Validated Surrogate Biomarkers

- Predict clinical benefit and can be used for regulatory approval of drugs in a defined context

- Provide increased confidence that the right dose and dosing schedule have been identified before a clinical outcome is observed

<table>
<thead>
<tr>
<th>Surrogate</th>
<th>Clinical Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c reduction</td>
<td>Reduced microvascular complications associated with diabetes mellitus</td>
</tr>
<tr>
<td>HIV-RNA reduction</td>
<td>HIV disease control</td>
</tr>
<tr>
<td>LDL cholesterol reduction</td>
<td>Reduced cardiovascular events</td>
</tr>
</tbody>
</table>
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Clinical Development

Clinical development is a staged process for evaluating an Investigational New Drug in humans following regulatory approval to conduct clinical trials.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Purpose</th>
<th>Dose</th>
<th>Typical number of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 0</td>
<td>PK</td>
<td>Sub-therapeutic</td>
<td>&lt;10 healthy</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Safety, PK</td>
<td>Ascending doses, starting low</td>
<td>10-100 healthy (unless cancer)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Safety &amp; efficacy</td>
<td>Therapeutic dose</td>
<td>100-300 disease</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Safety, efficacy, &amp; effectiveness</td>
<td>Therapeutic dose</td>
<td>300-3000 disease</td>
</tr>
<tr>
<td>Phase 4</td>
<td>Post-market surveillance in public</td>
<td>Therapeutic dose</td>
<td>Anyone seeking treatment from physician</td>
</tr>
</tbody>
</table>

Phase 0 trials are not widely used and are not required. They are only used if there is uncertainty about the predicted human PK and only a few healthy volunteers are administered a very low sub-therapeutic dose.

Phase 0

Human pharmacokinetic parameters

- Not often used (optional)
- If there is a sufficient degree of uncertainty about the predicted human PK
- Small number of healthy volunteers (<10)
- Low dose, sub-therapeutic
Phase 1 trials are usually the first time a drug is administered to humans and the primary purpose is to evaluate safety in a small number of healthy volunteers (unless for cancer trials). The dose starts low and is monitored carefully before ascending. The goal is to identify a safe dose range. Dosing is halted if any adverse events are observed. Ideally a therapeutic dose level is reached.

Biomarkers are more frequently being included in Phase 1 (if in patients with specific disease) for an early sign of proof of concept (POC).

Phase 2 trials involve patients with specific disease (100-300) with the objective of assessing safety and the effectiveness of the drug. Therapeutic dose levels are used to learn about adverse effects in the target population. Phase 2A aims to establish "Proof of Concept" and Phase 2B focuses on finding the optimal effective dose with minimal side effects. The goal is to learn about the effective dose range.

Phase 3 trials involve a larger number of patients with specific disease (300-3000) to confirm the therapeutic benefit. It focuses on efficacy benefit with minimal side effects which are tolerable and manageable, therapeutic dose, adverse effects in the larger target population, confirm effective dose(s), surrogate biomarker or clinical outcome, and PK & PD covariates such as age, gender, other drugs.
Phase 4
What are the long-term effects?

- Primary purpose: Post-market surveillance in the public (anyone seeking treatment from physician)
- Safety monitoring
  - Confirms common adverse events
  - Learn uncommon adverse events
- Confirm therapeutic benefit

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Clinical Trial Design
ABCS
- Assignment
- Blinding
- Comparison
- Sequence

There are 4 major elements in the design of a clinical trial. Each has an effect on the way trials are designed and interpreted.
Assignment

- First Come, First Served
- Randomized
  - Balanced
  - Stratified
    E.g. Sex, Previous Stroke

The assignment process is used to determine which subjects get which treatment.

The “First Come, First Served” assignment process covers a range of possibilities that will typically introduce bias e.g. giving active treatment to subjects seen in the morning and placebo to those seen in the afternoon, or alternating between active and placebo treatment. The main source of bias from this process is the loss of blinding. The investigator can guess which subjects are getting different treatments even if he/she is blinded to the actual assignment.

A randomized assignment process is considered the best method of deciding which subjects get which treatment. A list of random numbers is used to decide on treatments.

In order to ensure balanced allocation of treatments the number of subjects to be randomized is decided ahead of time and a balanced list of treatments is drawn up. This list is then randomly permuted and subjects drawn in turn from the permuted list. This ensures that the desired balance e.g. 50% in each of two treatment groups, is not affected by the randomization process.

If different sub-groups might have different responses it is common to stratify the randomization sequence. Separate sequences are drawn up for each sub-group e.g. one list for males and one for females.

Blinding

- Open
- Single Blind
- Double Blind
  - Double Dummy
- Triple Blind

Blinding is used to reduce bias. Bias can arise from both the investigator’s and subject’s expectation of the treatment effect.

Open trials are unblinded. They are still commonly used for marketing purposes but have little scientific merit. Single blind trials mean the investigator will know the treatment but the subject does not. Double blind trials mean both the investigator and subject are not aware of the treatment. Double dummy trials are used when two physically different treatments are compared e.g. tablet and inhaler treatments for asthma. Triple blind trials may occur if the randomization sequence is lost or misinterpreted – this means that nobody ever knows what treatment was given.

Blinded trials often become unblinded if the treatment has very prominent beneficial effects or adverse effects. This is very hard to prevent or adjust for in the analysis.
Good experimental science uses a control group to account for factors that might influence the outcome that are not experimentally assigned.

Within an active treatment arm it is usually desirable to learn about the relationship between intensity of treatment and outcome. The within active treatment control that is most widely used is the dose control i.e. there are two or more different doses arms in the active treatment group e.g. 100 mg, 200mg, 300mg.

Concentration control can be used to reduce the influence of random between subject differences in pharmacokinetics. By measuring concentration and individualizing the dose to reach desired target concentrations e.g. 10 mg/L, 20 mg/L, 30 mg/L, then the concentration effect relationship can be discovered.

If there is a biomarker (e.g. cholesterol concentration) that reflects the effect of the drug it can be used to control the intensity of treatment and reduce both pharmacokinetic and pharmacodynamic variability. Subjects are randomize to one or more target biomarker levels and the dose is adjusted to reach the target biomarker effect.

From a scientific perspective the best treatment control is to use a placebo i.e. an inactive substance. If there is genuine uncertainty about the effect of the active treatment then it is usually considered ethical to randomize to placebo.

However, if there is a standard treatment that would always be used because it is known to be effective then investigation of a new treatment may be in comparison with the standard treatment. This kind of trial is sometimes designed to show that the new treatment is no worse than the standard treatment – a non-inferiority trial.

If the standard treatment is given to all subjects then this would be considered an add-on trial design i.e. it looks for the effect of the new treatment in addition to the standard treatment. A placebo control group would receive the standard treatment.
The Placebo Effect

- Placebo is an inert treatment (such as a sugar pill or saline injection) that has no active therapeutic ingredient.
- Placebo effect can be a measurable positive health response attributed to the brain’s role in physical health.
- Placebo is an important control in a clinical trial.

Is this a genuine advertisement?


Placebo is an important control in a clinical trial:

- If there is genuine uncertainty about the active treatment effect
- If no standard treatment exists, placebo alone control used
- May be added to standard treatment

Sequence

- Parallel
- Crossover
- Titration
  - Forced
  - Flexible

The sequence of treatments can influence what is learned from a trial and the kind of bias that can arise. The parallel design has different treatments assigned to different groups of subjects. It is a good design for finding out the answer to the simple 'Does the drug work?' question but gives unclear answers to learning questions that ask about the shape of the dose response relationship of what dose is needed to achieve a particular effect.

A crossover design uses two or more treatments in each subject. This allows individual dose response curves to be observed and the true shape of the dose response relationship can be determined. The crossover design may also have an advantage in terms of statistical power. If it assumed that within subject variability is small then fewer subjects need to be studied to detect a treatment effect. There are several disadvantages of the crossover design. There may be a treatment carryover effect e.g. due to a drug with a long half-life. This would bias the response seen in a placebo treatment period that followed an active treatment period. If there is some systematic difference between periods e.g. the first treatment is given in the winter and the second treatment is given in the summer, then there may be a period effect that influences the response. Because each subject is asked to take several treatments there is a higher risk of dropout and loss of information from that subject.

Titration designs are a special kind of crossover design. These may involve giving a fixed sequence of doses ('forced titration') to each subject to learn about the dose response relationship. A more realistic titration design ('flexible titration') involves starting with a low dose and if the subject responds the dose is kept constant. The dose is only increased if the desired response is not reached.
Adaptive designs are an innovation that allow for adaptations or modifications to trial design after it has initiated without compromising the validity or integrity of the trial. Patient outcomes are monitored and adaptations made as the trial progresses on a pre-specified schedule and process. Modifications may include dose, sample size, drug, patient selection criteria or “cocktail” mix.

EGFR and ALK Inhibitors in Lung Cancer

- Drug resistance is the most important cause of treatment failure in cancer
- Cancer cells have intrinsic capacity to evade therapy
- This phenomenon is known as drug resistance
- Tumors may either be intrinsically drug resistant or develop resistance to anticancer drugs during treatment
- These case studies examine the development of receptor tyrosine kinase inhibitors for EGFR and ALK amidst the changing landscape of acquired mutations that cause drug resistance in non-small cell lung carcinoma (NSCLC)

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Adaptive Trial Designs
- Allows for adaptations or modifications on a pre-specified schedule as the trial progresses without compromising the validity or integrity of the trial
- Aim is to more quickly identify:
  - Drugs with therapeutic benefit
  - Appropriate patient population

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Slide 51
Driver mutations in Non Small Cell Lung Carcinoma (NSCLC)

- Genetic alterations subdivide NSCLC into different classifications
- Driver mutations in oncogenes such as the Epidermal Growth Factor Receptor (EGFR) are present
- Gene rearrangements in oncogenes such as EGFR and Anaplastic Lymphoma Kinase (ALK) are also present
- Identification of these oncogenes, their driver mutations or rearrangements and downstream effects allows the targeting of these pathways by drugs.
- Such personalized therapy has become an important strategy in combating lung cancer.

The Evolving Genomic Classification Of Lung Cancer

- EGFR and ALK mutations represent a fraction of the genomic subtypes present in NSCLC
  - EGFR activating mutations in ~10% Caucasian & ~40% Asian NSCLC patients, primarily seen in adenocarcinomas
  - EML4–ALK rearrangements in 2–7% of NSCLC patients, usually young never-smokers with adenocarcinoma
  - ALK-rearranged tumors are resistant to EGFR’s gefitinib and erlotinib

- EGFR and ALK receptor tyrosine kinase mutations represent a fraction of the genomic subtypes present in NSCLC
  - EGFR activating mutations present in ~10% Caucasian NSCLC’s and ~40% Asian patients, and are primarily seen in adenocarcinomas
  - EML4–ALK rearrangements occur in 2–7% of NSCLC patients, usually young never-smokers with adenocarcinoma
  - ALK-rearranged tumors are resistant to the EGFR’s gefitinib and erlotinib

- The underlying mechanism for a large proportion of NSCLC are unknown

Receptor Tyrosine Kinase Signalling In Cancer: The case of EGFR

Receptor tyrosine kinases (RTK’s) transmit signals from the cell surface into the cell that subsequently leads to changes in gene expression in the nucleus that result in cell proliferation and survival of cancer cells.

Activating mutations in EGFR cause the receptor to be constitutively active (ligand independent activation). This causes the downstream signalling pathway to be constitutively active resulting in proliferation and survival of cancer cells. An unexpected feedback loop was discovered in which constitutive activation of EGFR signalling also causes the upregulation of wildtype EGFR expression. In this case, the receptor is activated upon ligand binding and contributes to the amplification of EGFR signaling in the presence of ligand (EGF).
1\textsuperscript{st} Generation EGFR Inhibitors (EGFRi)

\begin{itemize}
\item First targeted drugs to enter NSCLC clinical use
\item Response rates were low & the drugs only led to modest improvements
\item Subsequent discovery of EGFR activating mutations in subgroups of patients associated with a favourable response to these EGFRi
\item Retrospective and prospective trials confirmed that the response rate in NSCLC patients with EGFR mutations is about 70-80%
\item Sensitizing mutations all found within the first 4 exons of the EGFR gene (Del19; L858R)
\end{itemize}

\begin{itemize}
\item Gefitinib (Iressa)
\begin{itemize}
\item Small molecule reversible EGFR inhibitor
\item Approved for advanced NSCLC with EGFR mutations after at least one prior chemotherapy regimen
\item FDA-approved in 2009 as a first-line treatment in NSCLC with EGFR mutation
\end{itemize}

\item Erlotinib (Tarceva)
\begin{itemize}
\item Small molecule reversible EGFR inhibitor
\item FDA-approved for locally advanced or metastatic NSCLC patients after failure of at least one prior chemotherapy regimen
\item Widely used as a first-line treatment in EGFR mutation positive NSCLC patients (Del19, L858R)
\end{itemize}

\end{itemize}

\begin{itemize}
\item First targeted drugs to enter clinical use for the treatment of lung cancer
\item Expectations that they would improve treatment outcomes for NSCLC patients but the response rate was low & they only led to modest improvements
\item FDA withdrew its initial approval after these disappointing clinical results
\item Subsequent discovery of EGFR activating mutations in subgroups of patients associated with a favourable response to these EGFRi
\begin{itemize}
\item Predominantly in patients of east-Asian origin, female, adenocarcinoma, and no history of smoking
\item Subsequent retrospective and prospective trials confirmed that the response rate to gefitinib or erlotinib in patients with EGFR mutations is about 70-80% and they have a significantly longer survival than those with wild-type EGFR when treated with EGFR TKIs
\item Sensitizing mutations all found within the first 4 exons of the EGFR gene
\begin{itemize}
\item Approx 90% of these EGFR mutations are either short in-frame deletions in exon 19 (Del19), or point mutations that result in a substitution of arginine for leucine at amino acid 858 (L858R)
\end{itemize}
\end{itemize}

\item Gefitinib:
\begin{itemize}
\item Iressa was approved and marketed from July 2002 in Japan, making it the first country to import the drug.
\item FDA approved Gefitinib in May 2003 for NSCLC as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies (third-line therapy).
\item June 2005 the FDA withdrew approval for use in new patients due to lack of evidence that it extended life
\item In Europe gefitinib was indicated since 2009 in advanced NSCLC in all lines of treatment for patients harbouring
\end{itemize}

\end{itemize}
EGFR mutations. This label was granted after gefitinib demonstrated as a first-line treatment to significantly improve PFS vs. a platinum doublet regime in patients harbouring such mutations. IPASS has been the first of four phase III trials to have confirmed gefitinib superiority in this patient population.  

- In most of the other countries where gefitinib is currently marketed it is approved for patients with advanced NSCLC who had received at least one previous chemotherapy regime.  
- August 2012 New Zealand approved gefitinib as first-line treatment for patients with EGFR mutation for naive locally advanced or metastatic, unresectable NSCLC.  
- July 2015 FDA approved gefitinib as a first-line treatment for NSCLC

- Erlotinib:  
  - FDA-approved in for locally advanced or metastatic NSCLC patients after failure of at least one prior chemotherapy regimen  
  - Has shown longer PFS than standard chemotherapy against major EGFR mutations (Del19, L858R)  
  - Shown to be effective in patients with or without EGFR mutations, but appears to be more effective in patients with EGFR mutations. Overall survival, progression-free survival and one-year survival are similar to standard second-line therapy (docetaxel or pemetrexed)  
  - Widely used as a first-line targeted treatment in EGFR mutation positive NSCLC patients (Del19, L858R)  
  - FDA has also approved erlotinib in combination with gemcitabine for treatment of locally
Acquired Mutations In Cancer Cause Resistance To EGFR inhibitors

Essentially all NSCLC patients with EGFR-activating mutations develop resistance to the gefitinib and erlotinib with a median duration of 10-13 months.

The most common resistance mechanism (occurs in 50–60% of patients) involves the development of the exon 20 T790M gatekeeper mutation.

2nd Generation EGFR Inhibitor (EGFRi)

Developed to address the emerging resistance to 1st Gen EGFRi in NSCLC.

Afatinib inhibits multiple mutant EGFR forms including: Del19, L858R, and exon 18 mutations (particularly G719)
- Also inhibits HER2 but has not performed well in breast cancer clinical trials
- Limited by dose limiting toxicity
- Recent preclinical data indicates that drug transporters restrict the oral bioavailability and brain accumulation of Afatinib.

Afatinib (Gilotrif)
- Small molecule irreversible EGFR & HER2 inhibitor
- Targets several EGFR mutations
- Approved for first line treatment of EGFR mutation positive (Del19, L858R) NSCLC
- Subsequently gained expanded approval for metastatic NSCLC whose tumors harbor uncommon (non-resistant) EGFR alterations in L861Q, G719X, and/or S768
- Limited by dose limiting toxicity
- Recent preclinical data indicates that drug transporters restrict the oral bioavailability and brain accumulation of Afatinib.
3rd Generation EGFR Inhibitor (EGFRi)

- Developed to address emerging resistance to 1st Gen EGFRi in NSCLC due to the T790M gatekeeper mutation
- FDA-approved for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR del19 or exon 21 L858R mutations as detected by an FDA-approved test
- Also approved for the second-line treatment of patients with metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed on or after EGFRi therapy

Osimertinib (Tagresso)
- Small molecule irreversible EGFR inhibitor
- Targets the T790M gatekeeper mutation
- First drug approved for the treatment of patients with the T790M gatekeeper mutation in NSCLC

Drugs Targeting ALK in NSCLC

- One of the breakthrough advances in lung cancer in the last decade
- ALK fusions initially found in a small subset (7%) of Japanese NSCLC patients
- The resultant fusion gene EML4-ALK has tyrosine kinase activity which causes increased cell proliferation due to activation of the ALK signaling pathway
- Other fusion partners also identified with different promoters causing constitutive expression of the fusion protein

Crizotinib (Xalkori)
- 1st gen small molecule inhibitor of ALK, c-MET and ROS
- Approved for late-stage NSCLC that express abnormal ALK gene and ROS1 positive NSCLC

Next Gen ALKis
- Developed to combat resistance to Crizotinib & limited CNS penetration
- Ceritinib, Alectinib & Brigatinib

- Crizotinib is one of the breakthrough advances in NSCLC treatment in the last decade
- ALK fusions first reported in 2007 in a small subset (7%) of Japanese NSCLC patients
- Fusion partner was echinoderm microtubule associated protein like-4 (EML4) gene, which is normally involved in microtubule formation
- The resultant fusion gene EML4-ALK has tyrosine kinase activity which causes increased cell proliferation due to activation of the ALK signaling pathway
- Other fusion partners also detected with most involving fusion of a promoter that causes constitutive expression of the fusion protein

- Crizotinib is a first gen inhibitor of ALK, c-MET and ROS
- FDA approved Crizotinib in August 2006 to treat certain late-stage (locally advanced or metastatic) NSCLC that express the ALK gene as shown by a companion molecular diagnostic test for the EML4-ALK fusion. In March 2016, the FDA approved crizotinib in ROS1 positive NSCLC. On October 2012, the European Medicines Agency approved the use of crizotinib to treat NSCLC that express the abnormal ALK gene
- Next gen ALK inhibitors have been developed to combat resistance to Crizotinib and address its limited CNS penetration (for treatment of brain metastasis).
Personalized therapy has become an important strategy in combating lung cancer.

Drugs Targeting Downstream Components Of The Receptor Tyrosine Kinase Signalling Pathway In Cancer

KRAS is the most frequently mutated oncogene in human cancers.
Slide 63

G12 is the most common KRAS mutation in cancer

RAS isoforms

Single base missense mutations in cancer


Slide 64

Drugs Targeting KRAS in Cancer

Drugging the “undruggable”

- KRAS is the most frequently mutated oncogene in human cancers
- The development of direct KRAS inhibitors has remained elusive despite more than three decades of intensive effort
- Recent progress has seen RAS directed agents entering clinical trials
  - Saliirasib: Dislodges the active RAS protein from the cell membrane, blocking the initiation of downstream signaling
  - MRTX849: Targets G12C mutation in KRAS that is frequently mutated in NSCLC and CRC (Mirati Therapeutics)

- Small molecule inhibitor of KRAS
- Targets G12C mutant form of KRAS
- In development for NSCLC and CRC
- Currently in Phase 1-2 clinical trials

Slide 65

Targeting BRAF & MEK In Cancer

- BRAF is most frequently mutated in melanoma (~60% have the V600E mutation)
- MEK 1/2 is downstream of BRAF and its activation leads to the activation of survival and proliferation signaling pathways
- Drugs that target a mutated form of BRAF and MEK 1/2 have been developed
- In melanoma, clinical trials have shown that resistance to BRAFi or MEKi occurs within 6-7 months. To address this, a combination of these two drugs was evaluated and approved in metastatic BRAF mutation-positive melanoma
- The drug combination has also been approved in NSCLC and anaplastic thyroid cancer

Drugs That Target BRAF & MEK in Cancer

**Dabrafenib (Tafinlar)**
- Small molecule inhibitor of BRAF
- FDA approved in 2013 for treatment of late-stage BRAF V600E mutant melanoma
- FDA approved in 2014 the combination of Dabrafenib & Trametinib for BRAF V600E/K mutant metastatic melanoma
- FDA approved in 2018 as an adjuvant therapy for BRAF V600E mutant advanced melanoma after surgical resection
- FDA approved in 2018 combination with Trametinib for BRAF V600-positive metastatic & unresectable anaplastic thyroid cancer

**Trametinib (Mekinist)**
- Small molecule inhibitor of MEK 1/2
- FDA approved in 2013 for treatment of late-stage BRAF V600E mutant melanoma

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Examples Of Short Answer Questions For The Final Exam

(a) Name ONE therapeutic drug that targets a receptor tyrosine kinase signalling pathway.

(b) Describe the drugs mechanism of action.

(c) Explain what patient population the drug you chose in part (b) is approved for.

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Test Question Example 1

(a) Name ONE therapeutic drug that targets a receptor tyrosine kinase signalling pathway.

(b) Describe the drugs mechanism of action.

(c) Explain what patient population the drug you chose in part (b) is approved for.
Test Question Example 2

(a) Explain the purpose of a Phase 1 clinical trial.

(b) How many patients are typically enrolled in a Phase 1 trial?

(c) Are biomarkers sometimes used in Phase 1 trials? Explain why.