Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

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MHRA approach to assessing early phase cancer study protocols

…in prinicpal no different to non-cancer trials!

- But
  - Do allow for use of patients rather than healthy volunteers
  - Expect a minimally efficacious dose in all patients
  - Allow accelerated dose escalation in some studies if justified
  - Agree to longer dosing period (until disease progression, unacceptable toxicity etc)
  - Accept the principle of maximum tolerated dose

We are starting to see new trial designs

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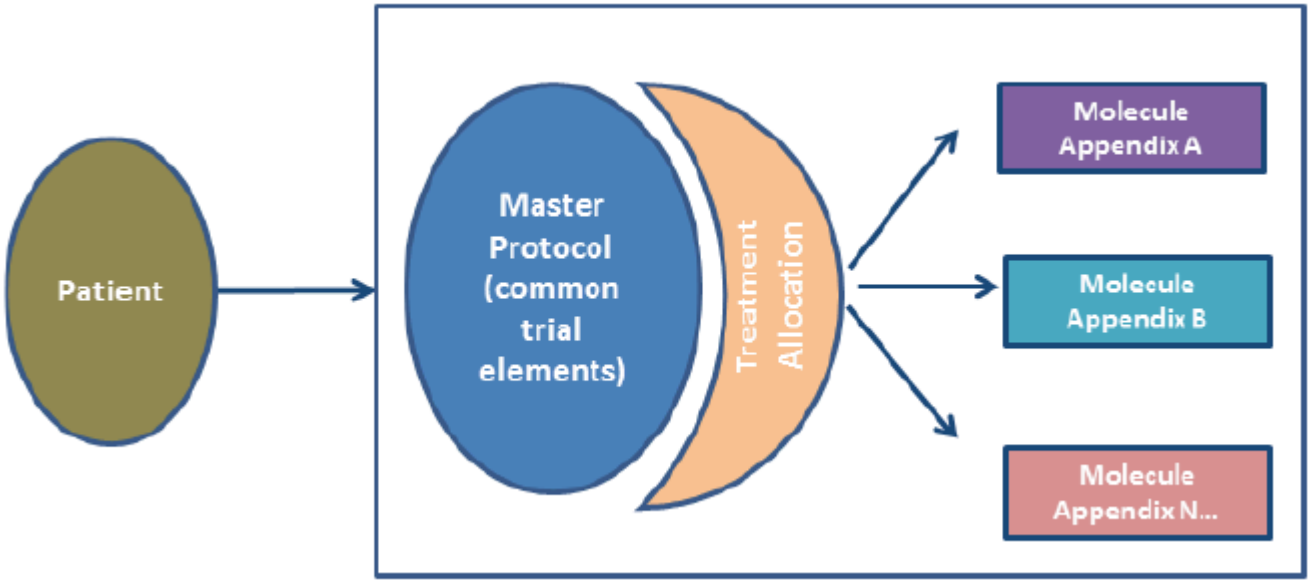
- Basket trials
- Umbrella trials
- Adaptive design
- Others…….

- We are starting to see them all and gain experience ourselves about what is acceptable and where the current limits may lie
- Discussions have been ongoing at the level of Clinical Trials Facilitation Group (CTFG), which now has an adaptive design subgroup
  - Aware that such designs are more common (and accepted) in the US and sponsors wish to do the same in the EU

- Umbrella and basket protocols are accepted by the MHRA
- Adapting such trials via an amendment is not always straight forward
- If the combination/additional IMP is discussed in the initial protocol and there is adequate rationale/safety measures:
  - The use of the IMP in future is acceptable (provided that there is no new information that prevents the safe use of the IMP/IMP combination at the time of the implementation)
- If the combination/additional IMP is added at the time of a substantial amendment: this may qualify as a ‘new’ trial.
  - An amendment qualifies as a new trial any time that the changes are not in line with the original research hypothesis.
  - Exceptions can apply on a case by case level

Example 1

- The Sponsor proposes to have a ‘Core protocol’ plus additional IMP-specific ‘parts’:
  - UK accepts that a core protocol could be common and used for several trials (the core protocol could contain: background, available treatment for the disease under investigation, safety reporting requirements, publication policy, data policy, unblinding, compliance assessment etc).
  - But the combination of the core protocol plus each IMP-specific part is considered to be a separate trial.
  - OR all parts are included in the initial CTA



- Master plus appendix A as one CTA / master plus appendix B as one CTA etc
- OR
- Master protocol plus **all** appendices as a single CTA

A modular, multi-arm, multi-part, first time in patient study to evaluate the safety and tolerability of XYZ (a MET inhibitor), alone and in combination with anti-cancer treatments

Multiple combinations all stated up front with a core protocol part – **accepted**

- A combination of XYZ with a small molecule PARP inhibitor.
- A combination of XYZ with a platinum based chemotherapy.
- A combination of XYZ with an anti-PD-1 or licensed anti-PD-L1 mAb.
- A combination of XYZ with a licensed anti-CTLA-4 mAb
- A combination of XYZ with a small molecule EGFR tyrosine kinase inhibitor/mAb.
- XYZ formulation switches.
- Potential effects of food on the PK of XYZ.

Example 2

- An initial protocol with the potential for “n” potential combinations is becoming the concern.
  - What is the real trial hypothesis and when will the trial be over?
  - “n” potential combinations are possible, the trial can run forever. How do we ensure safety and scientific rigour?

A phase 1b/2 open-label study to evaluate safety, clinical activity, pharmacokinetics and pharmacodynamics of XYZ in combination with other cancer immunotherapy in patients with advanced malignancies

- Initial CTA was
  - Combination A – XYZ plus 123

- Amendment proposed
  - Combination B – XYZ plus 456
  - Combination C – XYZ plus 789
  - Combination D – XYZ plus 123 plus ABC

The amendment was rejected as the new IMPs did not fit the original hypothesis or objectives and there were no comparisons between arms

Finally…..

The biggest barrier from our perspective is not coming to ask our advice early enough.

We can offer

- Scientific advice
- Regulatory advice
- Innovation office meetings - innovationoffice@mhra.gov.uk
- Email advice – clintrialhelpline@mhra.gov.uk
- Telephone assistance – 020 3080 6456

Questions?

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