Mid-recruitment trial redesign to incorporate genetic sub-types: the PICCOLO Trial

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Overview

• PICCOLO was originally designed in 2006 however after new molecular data emerged in 2008 a redesign was necessary

• This new data presented a number of challenges -

  • Urgent Safety Measure
  • Trial Redesign
  • Protocol Amendment
  • Acceptance and implementation of new design at trial sites
  • Implementation at CTRU
  • Initiation of prospective molecular testing service
PICCOLO Original Trial Design

Multicentre, phase III, chemotherapy trial in advanced colorectal cancer, academically led with industry financial support

n = 1269

IrCs
irinotecan + ciclosporin

Ir
irinotecan alone

IrPan
irinotecan + panitumumab

Ir vs IrCs
non-inferior efficacy
primary endpoint PFS at 12 wks

Ir vs IrPan
superior efficacy
primary endpoint OS
New Molecular Data

• Data released at the ASCO meeting in Chicago (30 May - 03 June 2008)
• Showed beyond reasonable doubt that patients with $K-RAS$ mutated colorectal cancer do not benefit from the addition of anti-EGFR monoclonal antibodies (cetuximab or panitumumab) to their chemotherapy.

Consequences for PICCOLO

Only patients with a $K-RAS$ wild-type tumour receiving irinotecan plus panitumumab (IrPan) stand to benefit.
How did we react?

30th May – 3rd June
- American Society for Clinical Oncology Conference

4th June
- CI returns from ASCO. Internal discussion with TMG

9th June
- DMEC agrees to Urgent Safety Measure and new protocol design
- 24-hour automated randomisation service suspended

10th June
- Urgent safety measure implemented
What is an Urgent Safety Measure?

• Regulation 30. in the The Medicines for Human Use (Clinical Trials) Regulations 2004 (amended 2006)

• (1) The sponsor and investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety.

• (2) If measures are taken pursuant to paragraph (1), the sponsor shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the licensing authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.
Urgent Safety Measure

• Office hours (9am – 5pm) telephone paper randomisation implemented
• Allowed only patients with known KRAS-wt to be randomised to IrPan
• No action thought to be necessary for patients with KRAS mutant tumours already receiving Pan (Pan shown to have no benefit in these patients rather than cause harm)
• All trial sites urgently notified of changes
Trial Re-design

$n = 1324$

**KRAS mutated or unknown**
- **IrCs** irinotecan + c’sporin
- **Ir** irinotecan alone

**KRAS-wt (c.12/13 & 61)**
- **Ir** irinotecan alone
- **IrPan** irinotecan + pan’mab

**Ir vs IrCs**
non-inferior efficacy
primary endpoint PFS at 12 wks

**Ir vs IrPan**
superior efficacy
primary endpoint OS
Protocol Amendment

**Action:**
- Substantial amendment to protocol and PIS
- KRAS specific consent required
- New registration process prior to randomisation
- TMG review & approval
- Protocol implemented from October 2008

**Challenge:**
- Day-to-day trial management still needed
- New system required additional testing
- Time pressures

**IMPACT:** More man-power needed
Implementation of new design at trial sites

**Action:**
- Acceptance of new design
- Local approvals
- Keep centres informed/training

**Challenge:**
- Not all study sites liked the new trial design (in particular not releasing KRAS status)
- Concern re delaying tmt
- Can be a lengthy process
- Teething problems with new protocol and KRAS testing

**IMPACT:** Knock on effect on recruitment
Implementation at CTRU

**Action:**

- Changes to CRFs to capture new data
- New administrative systems for central KRAS testing
- Change to randomisation system including registration

**Challenge:**

- Knock on effect on database – consider data collected for patients under original protocol
- Test, implement and maintain new system
- Ongoing queries from sites re KRAS status

**IMPACT:** Day-to-day management of trial – man-power
Initiation of prospective molecular testing service

**Action:**
- Consenting to *KRAS* testing
- Obtaining pathology blocks
- Performing *KRAS* testing
- Obtaining results for randomisation

**Challenge:**
- Time between patient identification and trial entry
- Delays at trial site when expediting tissue
- Failed tests need re-testing
- Time between patient registration and randomisation

**IMPACT:** Day-to-day management of trial
Increased communication with sites & central lab
Effect on recruitment

- New sites initiated and opened
- Negotiated extension with pharma partner and with CTAAC
- Continuous updates via trial newsletters
Points for Consideration

- Trials requiring a mid-recruitment redesign may become more common as further genetic advances are made
- Consider prospectively requesting consent for tumour collection
- Be realistic about manpower required for protocol writing and designing new systems – will affect regular trial activities
- Give ample training in new design, to ALL departments involved
- Minimise time between registration and randomisation – consider allowing testing in advance
- Make only minimal changes to CRF – knock on effect on database
- Easy identification of patients recruited under different versions of protocol (e.g. trial number)
- Consider any changes required to monitoring plan
Thank you

Any questions?

Acknowledgements: