Future-Proofing Academic Clinical Trials To Adapt For Regulatory Use

Andrew Embleton
15-Feb-2019
Outline

ICON6 regulatory submission

Rationale

EMA submission review

Draft recommendations
THE ICON6 EXPERIENCE
Six cycles of platinum-based chemotherapy
- Carboplatin/paclitaxel
- Carboplatin/gemcitabine
- Single agent platinum

Maintenance phase

Relapse >6 months after completion of first line platinum-based chemotherapy

Randomise 2 : 3 : 3

Arm A (Placebo)
- Chemotherapy + placebo
- Continue placebo

Arm B (Concurrent)
- Chemotherapy + cediranib
- Switch to placebo

Arm C (Maintenance)
- Chemotherapy + cediranib
- Maintenance cediranib

Treatment continued to 18 months or until progression (>18 for patients continuing to benefit)
Hazard Ratio 0.57 (0.45–0.74)
Log-rank p=0.00001

ECC 2013 Press Release: Biological Therapy with Cediranib Improves Survival in Women with Recurrent Ovarian Cancer

Women with ovarian cancer that has recurred after chemotherapy have survived for longer after treatment with a biological therapy called cediranib, according to new results to be presented Monday at the 2013 European Cancer Congress (ECC2013) [1].
Source Data Verification

Quality Checking

Blinded Independent Central Review
Chemotherapy phase  

Maintenance phase

Nausea

% of patients

Original  
Revised

Arm A  
Arm C

Grade 1  
Grade 2  
Grade 3  
Grade 4
Submission

EMA following retrospective verification

Opinion within 210 days

With a couple of opportunities for pauses where AZ answer questions

Opinion was negative at interim

GCP inspection was requested
GCP inspection

2.4. General comments on compliance with GMP, GLP, GCP

A request for GCP inspection has been adopted for the following clinical study D8480C0037. This was a routine GCP inspection. No specific concerns were known to have been identified by the assessment at the time of adoption of the inspection request. However, in this particular case, the fact that a national inspection conducted at one site in UK revealed critical findings in relation to safety and data integrity has been considered.

A total of four study sites were inspected (of 62 participating study centers). The inspections revealed several GCP findings. The main issues were related to:

- Oversight by the study sponsor which resulted in non-uniform conduct and reporting of data.
- The impact of post-unblinding activities on the reported data
- Lack of available documentation of the appearance of test and control product meant the blinding process is not verifiable.
- The safety profile was considered incomplete.
AstraZeneca withdraws cancer drug after 'differences of opinion' with regulator
2

RATIONALE
Academic research needed because industry…

1. Cannot explore all options
2. Rarely investigate less common diseases
3. Prefers short-term outcomes

*The most obvious differences to me are in terms of purpose and cost*
LITERATURE REVIEW
Looking for the interaction of two broad themes

Academic-led trials

Regulatory submission
<table>
<thead>
<tr>
<th>Topic</th>
<th>Count</th>
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<tbody>
<tr>
<td>Regional regulatory approval</td>
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<tr>
<td>Industry-academia interactions</td>
<td>4</td>
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<td>Academic drug discovery</td>
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<td>Trial conduct</td>
<td>2</td>
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<td>Data standards</td>
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REVIEW OF EMA LICENCE SUBMISSIONS
Withdrawal assessment report for Zemfirza (English only) 21/12/2016
EPAR review

Understand the problem

Retrieval

Search process
Results

1141 medicines processed > 386 results > **109 relevant**

Categorised as **major**, **minor** or **micro** involvement

25 (23%) **major** examples of academic involvement, 42 (39%) **minor** and also 42 (39%) **micro**
<table>
<thead>
<tr>
<th>Name</th>
<th>INN</th>
<th>Status</th>
<th>Indication</th>
<th>Therapeutic area</th>
<th>Trial use</th>
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<td>Severe Combined Immunodeficiency</td>
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<td>CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence</td>
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Approved

Majority

Approval rate comparable

Larger proportion that anticipated initial applications

Rare diseases – much more common, commercial interest?
Withdrawn

Split initial/extensions

Majority not rare

All had major objections due to GCP
Mylotarg (gemtuzumab ozogamicin, EMEA/H/C/004204)

ALFA-0701, conducted and sponsored by the Acute Leukemia French Association (ALFA) group
Also 5 non-commercial trials in supporting meta-analysis
  – ALFA-0701
  – SWOG-S0106
  – MRC AML15
  – NCRI AML16
  – GOELAMS AML2006IR

For the treatment of acute myeloid leukaemia in patients above 15 years of age

Some retrospective safety data collection needed

Approved
DRAFT RECOMMENDATIONS
ICON6

Regional, co-operative sponsors

Lead group oversight

Versioning of scales

Only enrol patients with Ethic’s approved, fully translated, consent forms

Formal IB communication

*Whether these can be generalised to most trials or not is yet to be determined*
More broadly

Academic-led trial use is possible

Gain more experience in collaboration on complex matters

Engage with the EMA – Scientific Advice

Awareness of potential issues – GCP inspection
Goal

Illustrate it is possible for successful submission of academic-led trials

Ultimately aiming to create a CONSORT-style framework of points to consider
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