Clinical Trial Design for Biomarkers

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Acknowledgements

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Randomised Clinical Trials are recognised as the gold standard for assessing new treatments.

But they only inform us of the average benefit for the population studied:

- Some patients on the control/standard treatment do very well.
- Some patients on the new/experimental treatment do very badly.

Randomised Clinical Trials cannot tell us whether:

- All patients benefit equally
- Whether a few patients benefit a lot (and perhaps in some there is a detriment)

As we move towards an era of targeted/individualised treatment, we need to identify any subgroups of patients who do well (or do badly).

We need develop and evolve trial designs.
Prognostic factors:

Are those baseline patient characteristics that indicate outcome irrespective of treatment

e.g.:
• Younger patients may survive longer
• Female patients may experience less toxicity
• Patients with larger tumours may metastasise sooner

JBR10 – adjuvant chemotherapy vs observation in completely resected NSCLC

Tsao et al, JCO 2007, 25, 5240-7
Prognostic factors:

Tsao et al explored the observation group (to avoid any interaction with treatment)

Showed that patients with p53 IHC –ve survive on average longer than those with p53 IHC +ve

But

This does not tell us who will benefit from treatment

Tsao et al, JCO 2007, 25, 5240-7

Predictive factors

Are those baseline characteristics that interact with the treatment to produce different outcomes in different subgroups

Interactions:
• Where those patients in a defined subgroup benefit from a treatment but
• Those patients outwith the subgroup do not benefit or the treatment has a detrimental effect
Predictive factors

Identifying predictive factors needs:

• A large dataset (an appropriate clinical trial)

• Pre-defined hypotheses and analysis plan (dangers of multiple testing and false +ve results)

• Definition of requirements for taking a predictive factor forward

JBR10: Vinorelbine plus cisplatin versus observation in resected non-small cell lung cancer

Wild-type RAS vs mutant RAS

HR=1.23
(95% CI:0.76 – 1.97)
P=0.40

Tsao et al, JCO 2007, 25, 5240-7
Subgroup analysis of JBR10 trial

Wild-type RAS

![Graph C](image1.png)

HR=0.69, p=0.03

Mutant RAS

![Graph D](image2.png)

HR=0.95, p=0.87

Interaction p=0.29

Tsao et al, JCO 2007, 5240-7

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K-ras mutations and benefit from cetuximab in advanced colorectal cancer

![Graph A](image3.png)

HR 0.55, p<0.001

![Graph B](image4.png)

HR 0.98, p=0.89

Interaction p=0.01

Karapetis et al. NEJM 2008, 359, 1757-65
Once we’ve found a likely predictive marker we need to:

• Classify (standardise method, define cut-offs (continuous variables may correlate with outcome)

• Validate (to assess predictive accuracy – sensitivity and specificity)

Three clinical trial designs have been developed to assess biomarkers:

1. Stratified
2. Enrichment
3. Strategy
Stratified design: The MARVEL trial

Hypotheses
- In the FISH+ve group erlotinib expected to be better than pemetrexed
- In the FISH-ve subgroup pemetrexed expected to be no worse (and possibly better) than erlotinib

Wakelee H et al, Clin Lung Ca 2008, 9, 346-51

Stratified

Benefits:
- All patients that can be classified are included
- The outcome can be looked at in an unbiased way
- Tests efficacy (effect under ideal conditions)
- Confirms the treatment effect in the marker group and the non-marker group
Stratified Issues:

- Some of the treatments may not be appropriate for non-marker patients
- Interim analysis stopping rules may need to include an option to stop the trial in one of the subgroups
- May need a much larger number of patients as a normal trial

Enrichment – The FLEX trial

- 1861 patients screened
- 1688 with tumour specimen suitable for assessment of EGFR expression
- 1442 EGFR-expressing tumours
- 723 excluded
  - 183 did not meet inclusion criteria
  - 79 refused to participate
  - 59 other reasons
- 4 EGFR status unknown
- 1125 randomly assigned
- 557 allocated to chemotherapy plus cetuximab
  - 446 given chemotherapy plus cetuximab
  - 13 not given study treatment
  - 9 given chemotherapy only
- 568 allocated to chemotherapy
  - 530 given chemotherapy
  - 38 not given study treatment

Enrichment

Benefits:
• Not treating those who are not expected to benefit from the treatment
• Limiting the size of the trial

Enrichment

Issues:
• Need the marker to identify the subgroup who will benefit with reasonable accuracy (If treatment genuinely improves outcomes in a subgroup of patients, but the marker does not identify that subgroup, a beneficial treatment could be abandoned)
• Does the treatment actually benefit all patients (cannot assess what is the best treatment in the non-marker group)
Strategy: The ERCC1-based customized chemotherapy trial

Cobo et al, JCO 2007, 25, 2747-54

Strategy

Benefits:

Tests **effectiveness** (better reflects what happens in clinical practice)

Only those in the experimental arm need have marker status
Strategy

Issues

Patients in different arms receive the same treatment – this dilutes any difference seen

The targeted treatment may be better irrespective of marker

Missing marker information (patients assessable in the Cobo trial: standard arm: 95%, genotypic arm: 76%)

Knowledge of the marker may influence treatment, follow-up, or assessment of outcome (e.g. response)

The $64,000 question: which design?

Assuming that you have

1. Identified a significant interaction (marker + treatment)
2. Decided on the best cut-off point
3. Validated the interaction in an independent dataset
4. Confirmed that the marker is quick, cheap, reliable and reproducible

then….
The $64,000 question: which design?

- If the treatment is expected to have no effect (or much less of an effect) in the non-marker group – **stratified**
- If the treatment is not be appropriate or may be detrimental in the non-marker group – **enriched**
- If you want to compare the concept of targeted treatment against standard (non-targeted) treatment - **strategy**

**Challenges**

- Defining a useful predictive factor (needs large datasets, pre-defined hypotheses, validation, classification, etc)
- Selecting the right trial design, clarifying the sample size, and analyses to be undertaken
- Accruing sufficient patients (need large numbers of patients from smaller subgroup population) to avoid false +ve or false –ve results
- Understanding the results (not over-interpreting)
Conclusions

Testing targeted treatments adds an extra complexity to running clinical trials

Incentive to collaborate globally

Proceed carefully

Get expert help!

The key players

Cindy Billingham, Mark Buyse, Laurence Collette, Boris Freidlin, Wenyu Jiang, Ed Korn, Sumithra Mandrekar, Lisa McShane, David Ransohoff, Dan Sargent, Patrick Therasse, Rich Simon (capt)
Key papers:


- Sargent et al. Clinical trial designs for predictive marker validation in cancer treatment trials. JCO 2005, 23, 2020-7

- Tsao et al, Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in NSCLC. JCO 2007, 25, 5240-7

- Cobo et al. Customizing cisplatin based on quantitative excision repair cross-complementing 1 mRNA expression. JCO 2007, 25, 2747-54
IPASS - Gefitinib or carboplatin/paclitaxel in pulmonary adenocarcinoma

Mok TS, et al. NEJM 2009, 361, 947-57
IPASS designed as a non-inferiority trial to see if gefitinib was as effective as chemotherapy.

Patients selected, not on EGFR status, but on clinical criteria (never-smokers, female, adenocarcinoma, Asian) as a high proportion of these have an EGFR mutation but

Subgroup (superiority) analysis showed benefit for gefitinib in EGFR mutation +ve patients, and a detriment in 176 mutation –ve patients.

Is it now possible to run confirmatory trials giving gefitinib to EGFR mutation –ve patients???

Health warnings:

1. Getting the design wrong can affect future research
2. Don’t run before you can walk!

[Diagram showing patient treatment flow and survival analysis graph]