Considerations for design

- RCT remains the gold standard
- n-of-1 design: this is a sequence of different treatments in one and the same patient.
  - Has the feel of cross-over design
  - Question: how does that work in oncology?
- Play with the type I error (or even type II error). For example:
  - One sided testing: can be acceptable
  - Higher type I error (alpha): this will never be found, because the trial will not be repeated
  - More optimistic alternative hypothesis: this has the same practical effect as increasing the type II error (beta): only a really strong improvement has good chances of being identified. Look more at the confidence interval.
Considerations for design

- Single-arm/non-comparative approaches
- The fact of having some responses is an improvement in itself
- The fact of stopping progression is an improvement in itself
- Robust historical data is available with small between trial variability (not likely, but happens)
There is no current standard ...

I would then (still) suggest a randomized approach with either a Phase II selection design, or a play-the-winner (adaptive randomization) approach.

Other cases:

• Maybe it is worthwhile to incorporate in the plans a trial / decision point where disagreement is settled.

• If the standard is wait-and-see, that can be randomized against.
Example of evolution: how we see Phase II trials

- Trying to improve the Positive Predictive Value
- Accommodate many objectives: moving to an amalgam of approaches

Seymour et al. CCR 2010
Suggestion

• When there are less patients ... then per patient more information needs to be collected

• Patient as their own control:
  ▪ Make trials where patients are followed much longer, following patients and their consecutive treatments ‘forever’. (Similar to n-of-1 approach)
  ▪ Obtain detailed information of disease evolution (e.g. tumor measurements) pre-treatment. Because rare cancer trials are done in specialized hospitals, this may be achievable. Can give much more info than e.g. usual RECIST (which has 1 baseline).
Alternative endpoints

• Continuous endpoint of change in tumor size
  ▪ Instead of binary response
  *Karrison et al, Design of Phase II Cancer Trials Using a Continuous Endpoint of Change in Tumor Size: Application to a Study of Sorafenib and Erlotinib in Non–Small-Cell Lung Cancer, JNCI, 2007*
  *Wason et al, Reducing sample sizes in two-stage phase II cancer trials by using continuous tumour shrinkage end-points, EJC, 2011*

• “Growth modulation index”: ratio of time to progression under previous treatment relative to time to progression under new treatment
  ▪ Paired failure-times within each treated patient
  *Mick et al, Phase II clinical trial design for noncytotoxic anticancer agents for which time to disease progression is the primary endpoint, CCT, 2000*
Suggestion (continued)

- Consider drawing from other cancer types with similar expression of genetic damage
  - EMA guidance: “... For example, in studies investigating the activity of a compound targeting a specific, molecularly well-defined structure assumed to be pivotal for the condition(s), it might be possible to enrol patients with formally different histological diagnosis, but expressing this target. ...”
Suggestion (continued)

• Make more use of interim testing (or adaptive designs)
  - Usually in rare cancer types accrual is somewhat slower/longer, so more information on the enrolled patients is available at time of interim analysis, as compared to quickly enrolling trials
  - Any predefined plan of taking decisions can be investigated for its operating characteristics
Alternative designs

• Cross-over design
  - Paired failure-times within each treated patient
  - Underlying assumptions for carrying out such studies almost never valid in cancer studies (carry-over effect)

• 3-stage design

Honkanen, A three-stage clinical trial design for rare disorders, SiM, 2001
From Gupta et al.
Acknowledgements

• Consensus notes from Gynecologic Cancer Intergroup Harmonization Committee, Statistical Subcommittee (ASCO 2011, Jim Paul et al.)
• Catherine Fortpied
Reading

• A framework for applying unfamiliar trial designs in studies of rare diseases, S. Gupta et al., Journal of Clinical Epidemiology 2011
• Clinical trials and rare diseases, S. Lagakos, NEJM editorial 2007
• Trials in rare diseases: the need to think differently, Billingham et al. Trials 2011
• Evidence-Based Medicine for Rare Diseases: Implications for Data Interpretation and Clinical Trial Design, Behera et al. Cancer Control 2007
Back-Up
Looking for new common ground

• Trials with a high level of patient startup work
  ▪ Screening many to obtain some eligible patients
  ▪ Splitting according to markers
  ▪ High workload to include patients
  ▪ Timelines to enter a patient

• Think about:
  ▪ Trials spanning several phases of development
  ▪ Trials with multiple additional analyses / endpoints
  ▪ TR analysis and planning of such analysis
  ▪ Biobanking
  ▪ Tools to perform complex logistics
Buzzword: Adaptive designs

• We are learning to plan and run these complicated trials in an acceptable way
  ▪ Appropriate use of IDMC
  ▪ Appropriate use of adaptive elements in the design
• Word of warning: adaptive designs are not the solution to manage the unexpected. But adaptive elements can be very interesting to manage the complicated.
• We are already using many adaptive ideas in our trials (all phases).
• Keys here are: think and discuss upfront and monitor during the trial
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Regulatory Evidence</th>
<th>Study Design</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>Clinical benefit</td>
<td>Randomized</td>
<td>Direct measure of benefit, easy, precise</td>
<td>Large studies, crossover / followup Tx affects, noncancer deaths</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Clinical benefit</td>
<td>Randomized, blinded</td>
<td>Patient perspective of direct clinical benefit</td>
<td>Blinding hard, missing data, clinically relevant effect, validated tools lacking</td>
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<tr>
<td>DFS</td>
<td>Surrogate</td>
<td>Randomized, blinded, blinded review</td>
<td>Smaller, shorter</td>
<td>Not stat. validated as surrogate for OS / not precise, open to bias / many definitions</td>
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<tr>
<td>RR</td>
<td>Surrogate</td>
<td>Blinded, blinded review</td>
<td>1-arm possible, smaller, shorter, attributable to drug</td>
<td>No direct measure of benefit / no comprehensive measure of drug activity / only subset of benefiting pats.</td>
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<tr>
<td>CRR</td>
<td>Surrogate</td>
<td>Blinded, blinded review</td>
<td>1-arm possible, smaller, shorter, durable CR = benefit</td>
<td>No direct measure of benefit / no comprehensive measure of drug activity / small subset of benefiting pats.</td>
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<td>PFS</td>
<td>Surrogate</td>
<td>Randomized, blinded, blinded review</td>
<td>Smaller, shorter, SD included, crossover / other Tx not affecting, objective &amp; quantitative</td>
<td>Not stat. validated as surrogate for OS / not precise, open to bias / many definitions / frequent assessments / need to balance timing x arms</td>
</tr>
</tbody>
</table>
Evolution of endpoints leading to EMA oncology approvals

Per F Pignatti presentation at EORTC advanced course, September 2010
Alternative designs (cont’d)

• Bayesian design, formally incorporating historical data into the design
  - Involve prior beliefs which may not be universally accepted
  - If we conduct a small trial, the choice of the prior may carry heavy weight