Oxford University Hospitals NHS
NHS Foundation Trust

CRMs from a clinician perspective
Continual reassessment or continual stress?

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Potential conflicts of interest

- I am the CI of RomiCar and am leading the development of the CHAPTer study
- Christina Yap has brainwashed me…..

Aims of this presentation

- For statisticians to go easy on poor clinicians
- To give you tools to persuade clinicians of the benefit of CRMs

My background

Double maths A-level (but mechanics)
Last time I did stats was GCSE (and I didn't enjoy it…..)

Standard medical training (cursory medical stats course)
Registrar training in haematology in Oxford
Managed patients on trials but
No experience in developing proposals

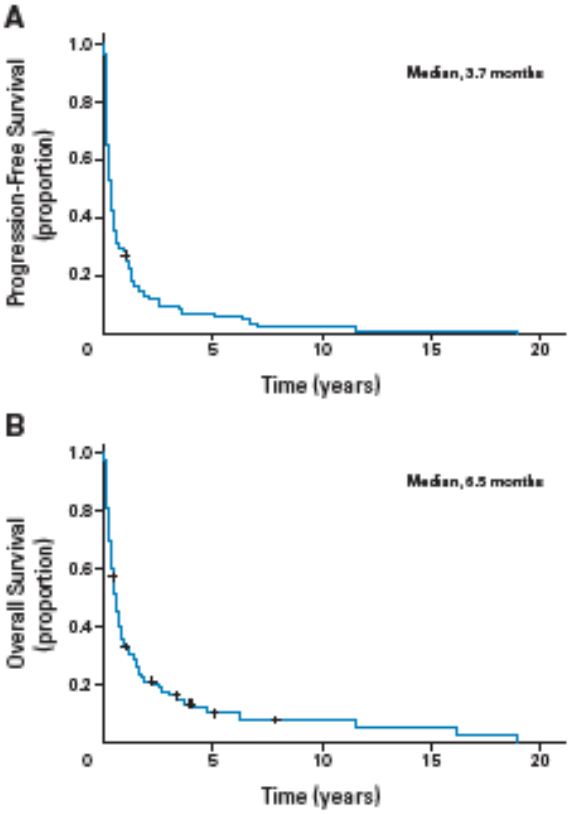
DPhil in molecular biology of the Reed-Sternberg cell

Appointed as a consultant 2010 on lymphoma team with remit to increase trials portfolio

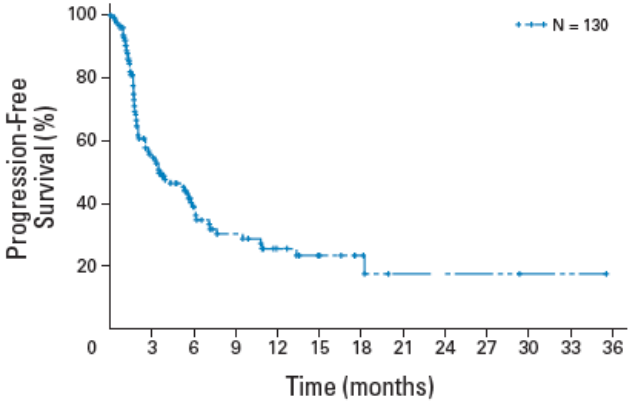
At this stage: 'what's does a p value mean….?'

My first trial idea: RomiCar

Relapsed T-cell lymphoma a clear area of unmet need
Mak *et al* JCO (2013)



Romidepsin licensed in US (not Europe)
ORR 25% but CRs did very well
HR23B MIGHT predict activity



Hypothesis:

Can we improve benefit with romidepsin by adding carfilzomib and see if HR23B identifies those likely to respond?

Initial proposal

- 3+3 design
- Aimed to find the MTD in relapsed / refractory PTCL
- Then cohort expansion to assess efficacy using single stage A'Hearn design

Then I had a teleconference with Christina…….

The conversation:

Christina: ‘why don’t you use a CRM design?’

Me: ‘What’s a CRM design?’

Christina: ‘it uses Bayesian methodology and posterior probabilities to better estimate the MTD’

Me: ‘???????’

Christina: ‘3+3 are not good at getting the right MTD; CRMs are better and more efficient and you’re more likely to get the trial funded’

Me: ‘OK’

Clinicians want their trials funded first go!

The next conversation

Christina: ‘Well done for getting the trial accepted’

Me: ‘Thank you’

Christina: ‘now we need to build the model. Can you guess what the DLT rate is for each dose level please?’

Me: ‘What do you mean…… ***guess***?’

Clinicians do not like to guess!

Need to reassure

The model

Dose Level	Romidepsin dose (days 1, 8, 15)	Carfilzomib dose (days 1, 2, 8, 9, 15, 16)	Estimated DLT rate
1	8mg/m^2	20/36mg/m^2	5%
2 Starting Dose	10mg/m^2	20/36mg/m^2	10%
3	10mg/m^2	20/45mg/m^2	15%
4	12mg/m^2	20/45mg/m^2	25%
5	12mg/m^2	20/56mg/m^2	35%
6	14mg/m^2	20/56mg/m^2	50%

How the CRM has helped RomiCar -1

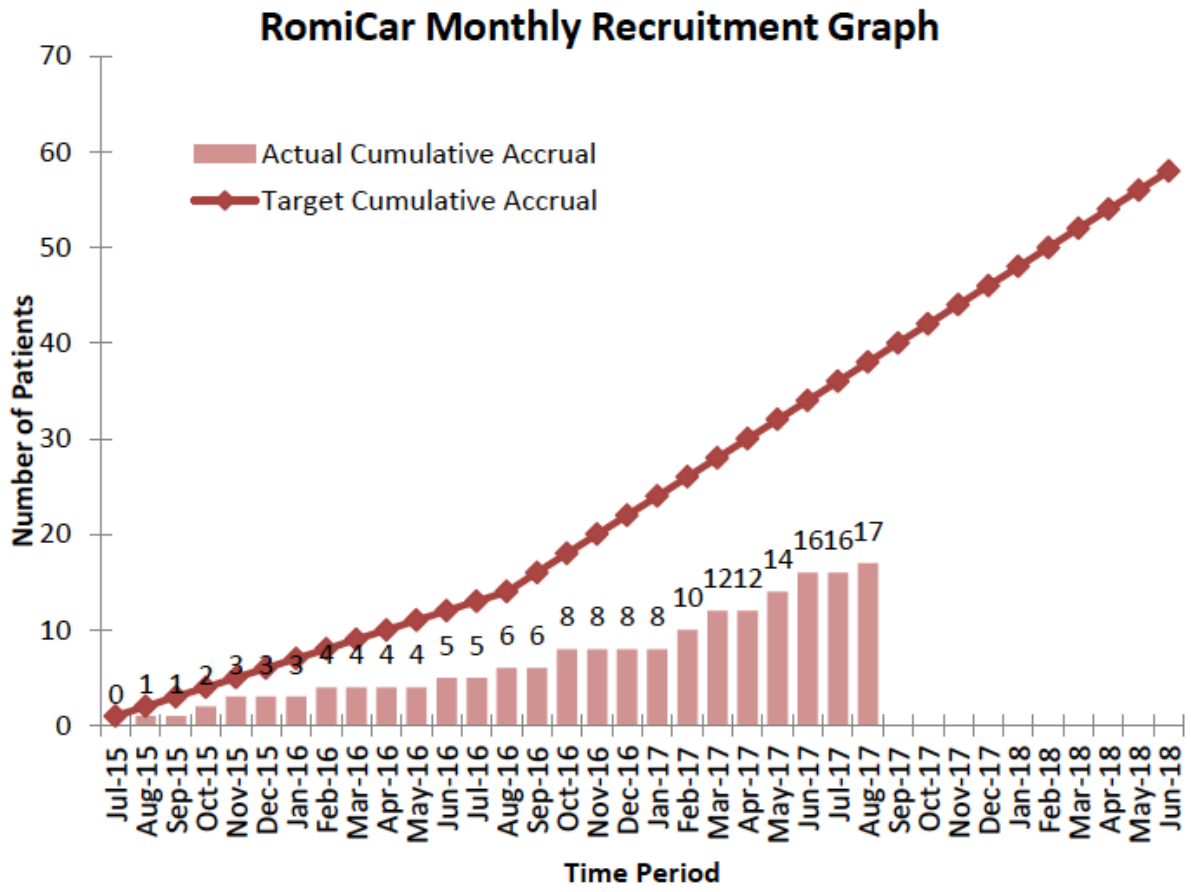
One of the first patients dosed should have been dosed at DL2 but actually received DL1 – *and they had a DLT*

What an incompetent trial site that must have been….

However the CRM could incorporate the data and inform the model.

I was now getting convinced how a CRM could improve efficiency

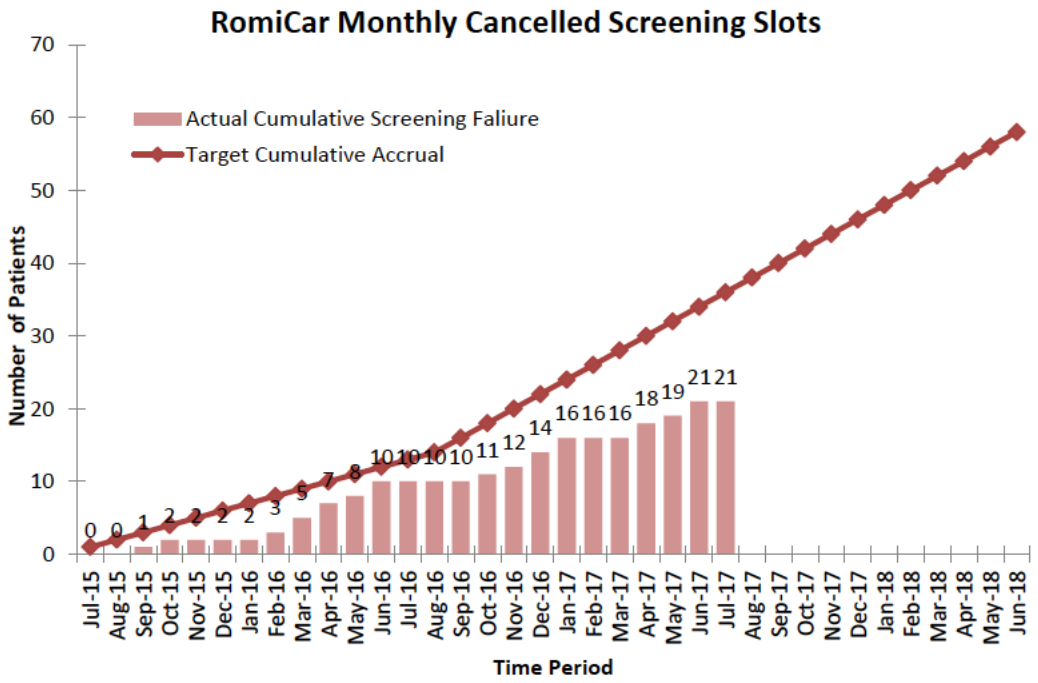
Next problem…..Recruitment



Oh dear!

Why?

Screen Failures



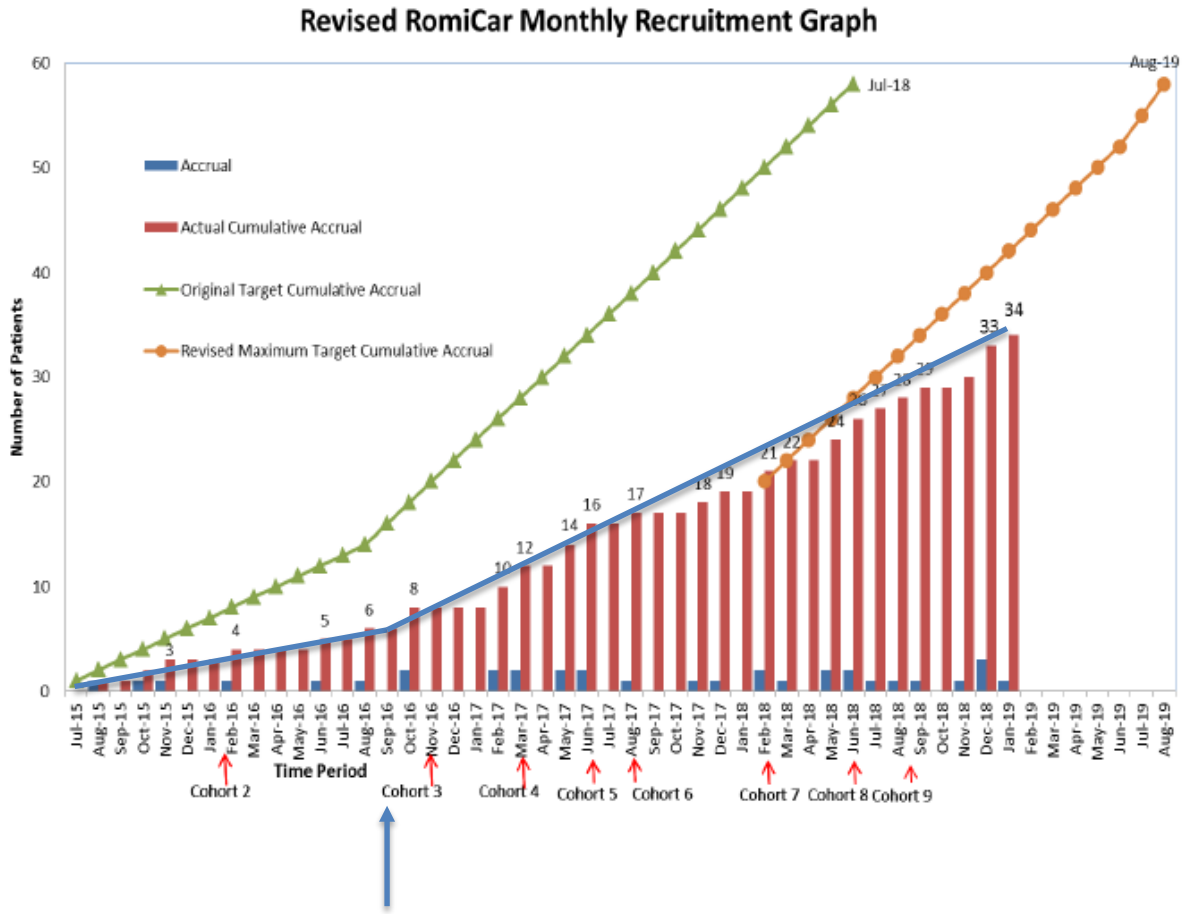
We were having more screen failures than patients getting to treatment!
T-cell lymphoma is aggressive disease
We only initially had 3 slots open per cohort
Many sites were ringing for slots but when one came up, they were no longer eligible

Could the CRM come to our rescue……

Yes! (as part of a package of measures)

- We amended the protocol to not absolutely require a biopsy at relapse
- We adjusted the CRM to allow:
  - Increasing the slots (up to 8) potentially varying what dose level they were assigned to
  - Not more than 3 patients will be exposed to a dose level that has not been determined as tolerable
  - So if investigating a higher DL, 3 patients will be assigned to that and any remainder will be assign to the DL below

Did it work……?



Amendment

Prior: average duration of cohort – 8 mo

After: average duration of cohort – 3.5 mo

Practical working

- As with any trial, regular TMGs
- Statistician always at the meeting
- Required a ‘dumbed down’ explanation of where we were with the model
- Very helpful dose transition pathways – makes the potential outcomes more concrete

Example of transition pathways

Path	Dose in Cohort 2	Num DLT in Cohort 2	Dose in Cohort 3	Num DLT in Cohort 3	Dose in Cohort 4	Num DLT in Cohort 4	Dose in Cohort 5
1	2	0	3	0	4	0	4
2	2	0	3	0	4	1	4
3	2	0	3	0	4	2	3
4	2	0	3	0	4	3	2
5	2	0	3	1	3	0	3
6	2	0	3	1	3	1	2
7	2	0	3	1	3	2	2
8	2	0	3	1	3	3	1
9	2	0	3	2	2	0	2
10	2	0	3	2	2	1	1
11	2	0	3	2	2	2	1
12	2	0	3	2	2	3	1
13	2	0	3	3	1	0	1
14	2	0	3	3	1	1	1
15	2	0	3	3	1	2	1
16	2	0	3	3	1	3	1
17	2	1	1	0	2	0	3
18	2	1	1	0	2	1	2

I am a happy PI thanks to CRM

- Has enabled ‘dodgy’ patients to be included in the analysis
- Has enabled us to increase recruitment
- Has enabled more slots which has helped keep PIs interested in the study and
- Hopefully it’s benefiting patients by recruiting more in a timely way
- Hopefully it will help to satisfy Bloodwise and pharma…..

Have there been downsides?

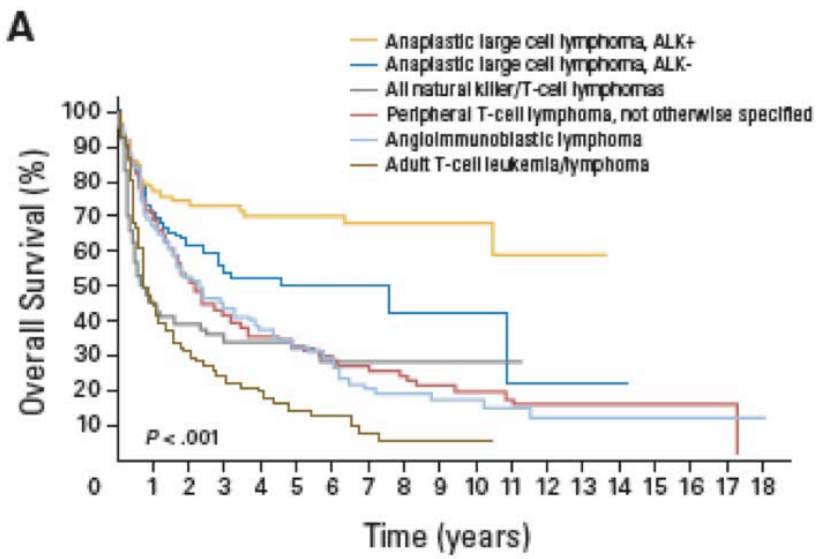
Not many

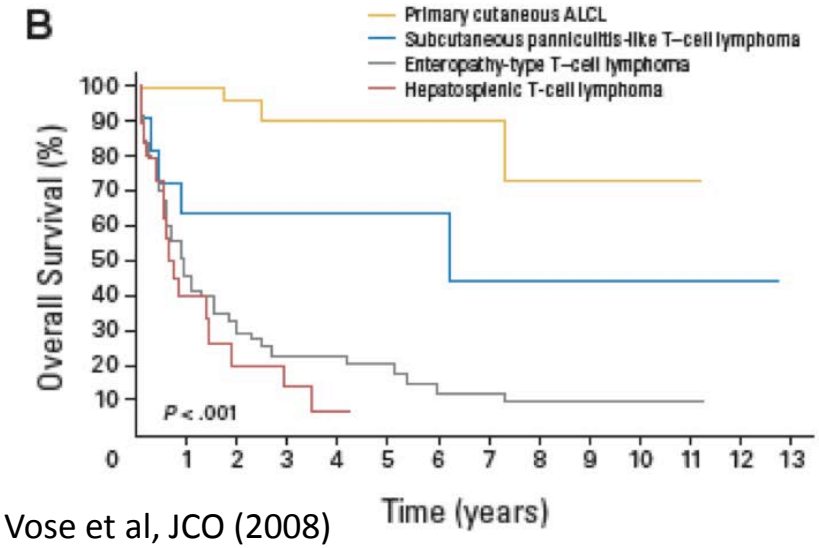
As phase 1 progressed, it was a little unclear when we would be calling the MTD which made it hard to reassure funding bodies about trial progress.

My 2nd experience of a CRM – ADCT301

- Commercial trial of a new ADC in R/R lymphoma
- Slot driven approach
- Very flexible in allowing expansion of doses ‘where clinical activity had been observed’
- In practice, there always seemed to be a slot
- Don’t know where they got their money from!

In for a penny, in for a pound – CHAPTer study





Vose et al, JCO (2008)

Whilst RomiCar is conquering relapsed T-cell lymphoma, what about the front line setting?

Outcomes are poor

ASTX660 is a new anti-IAP inhibitor which shows activity against T-cell lymphoma as a single agent.

Non-overlapping DLTs with CHOP chemotherapy (the SOC)

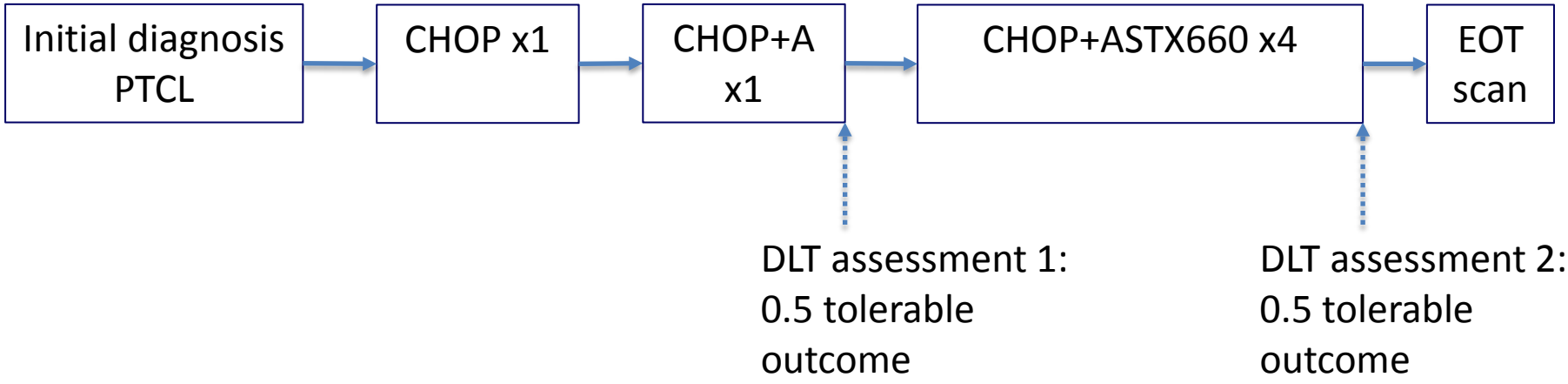
Brave trial….?

ASTX660 never been given with chemo before
Front line setting in which some patients are cured
CHOP has some early tox: FN, alopecia, GI upset
Also some cumulative tox: cardiac, fatigue, neuropathy

But a DLT period of 6 cycles (6x3 = 18 weeks) too long to be feasible as sole DLT period

Plus….I had just been on a course about TITE CRM designs…

TITE CRM – could this help?



In order to recruit at a higher dose level:

- 3 tolerable outcomes need to be obtained with
- At least 1 patient having finished all 6 courses without a DLT

Final thoughts

- Clinicians like well trodden paths which they understand
- But they also like running trials that work and get funded
- Clinicians like being in control so may struggle with handing a lot of control to the statistician
- But this can be overcome by good communication, explanations of the methodology and material such as dose transition pathways
- Finally I am a convert to CRM! It has helped RomiCar no end

Thank you!