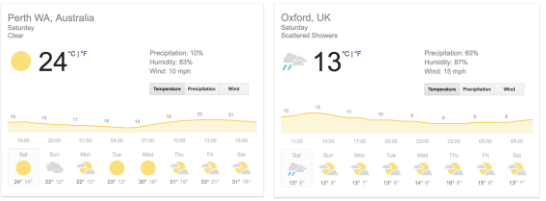
Early Phase Clinical Trials

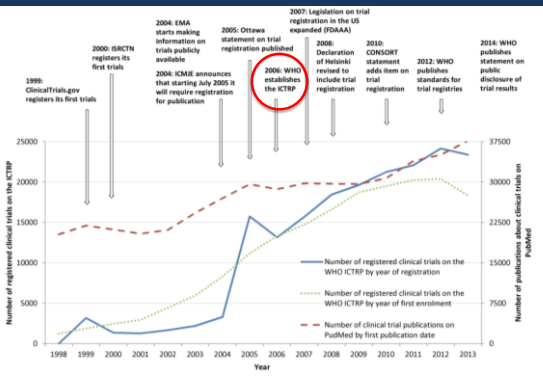
Murali Kesavan
Haematology Fellow

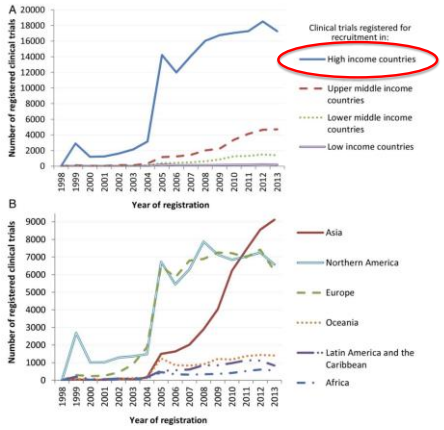


Overview

I. Clinical trials
II. Early phase trials
III. Benefits v risks
IV. The *therapeutic misconception*
V. Challenges

Clinical trials





NHS Research

Approximately **1%** of the population

OUH NHS Trust

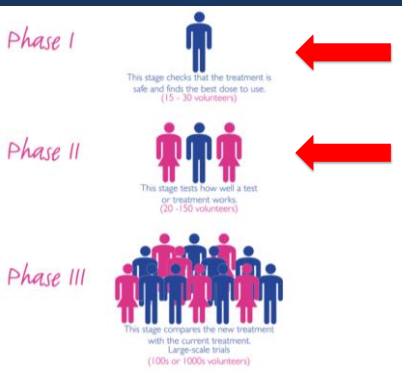
Research studies

Year	Total number of studies recruiting	Commercial contract studies
2013/14	380	-
2014/15	411	78
2015/16	463	99
2016/17	505	105
2017/18	517	110
% change from 2016/17	2.4%	4.8%

Participant involvement in research studies

Year	Total participants in studies	Participants in commercial contract studies
2013/14	18442	-
2014/15	17827	652
2015/16	21169	1764
2016/17	22154	1898
2017/18	20937	1729
% change from 2017/18	-5.5%	-8.9%

Early phase clinical trials



Ethical aspects

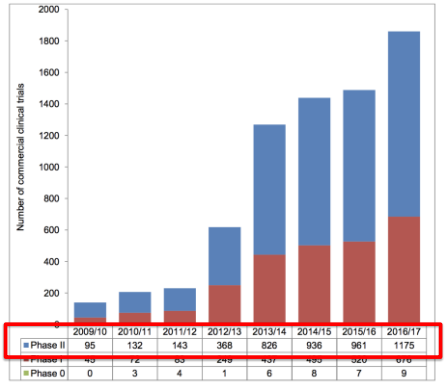
- The research objectives and underlying ***scientific rationale*** must be strong
- ***Therapeutic intent*** is central
- Enrolment in an early phase clinical trial is an ***option***
- The availability of ***tumor material*** at the time of enrolment in an early phase trial will enable the maximal knowledge to be obtained from the study
- The inclusion of ancillary/biological studies (tumor analysis and pharmacodynamic (PD) studies) increases the ***scientific value*** of early phase clinical trials, and thus, the future use of the drug
- Information on PD biomarkers can be obtained ***noninvasively*** or by blood sampling

Moreno et al ***Nature Reviews***. Clinical Oncology; Aug 2017, 14(8): 497-507

Ethical aspects

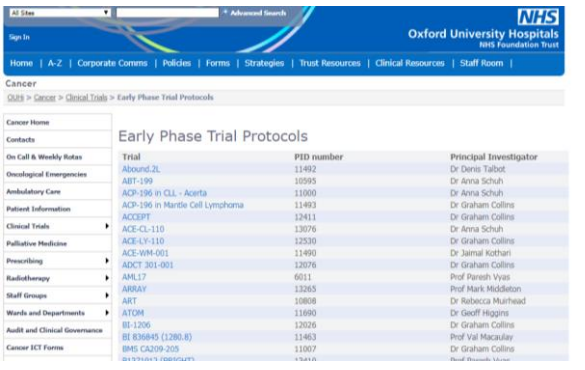
- Experimental
- Outcomes **unknown**
- Based on pre-clinical data (single cell studies, animal studies, biologic models)
- **First in human**
- Commercial v university sponsored
- Global v national > slot driven

Figure 4. Early Phase commercial contract and collaborative trials active across the NIHR translational infrastructure



	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
Phase II	95	132	143	368	826	936	961	1175
Phase I	45	72	83	249	457	495	520	676
Phase 0	0	3	4	1	6	8	7	9

OUH early phase trials

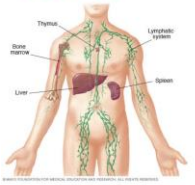


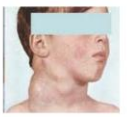
- Approximately **90 trials** currently open across oncology and hematology

Benefits v Risks

Lymphoma

Non-Hodgkin's Lymphoma Disease Overview





- Non-Hodgkin's lymphoma (NHL) is a cancer of the lymph node
  - It can also involve the bone marrow, liver and spleen
- B-cell NHL comprises of multiple subtypes: DLBCL, follicular lymphoma (FL), are the two most common
- Fifth leading cancer cause of death in the US

Hu-5F9G4

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1b/2 Trial of Hu5F9-G4 in Combination with Rituximab in Patients with Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma
Protocol Number:	5F9003
Investigational Products:	Hu5F9-G4 and rituximab
Indication:	Non-Hodgkin's Lymphoma
Development Phase:	1b/2

Benefits v Risks

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma

Ranjana Advani, M.D., Ian Flinn, M.D., Ph.D., Leslie Popplewell, M.D., Andres Forero, M.D., Nancy L. Bartlett, M.D., Nilanjan Ghosh, M.D., Ph.D., Justin Kline, M.D., Mark Roschewski, M.D., Ann LaCasce, M.D., Graham P. Collins, M.D., Thu Tran, B.S., Judith Lynn, M.B.A., James Y. Chen, M.D., Ph.D., Jens-Peter Volkmer, M.D., Balaji Agoram, Ph.D., Jie Huang, Sc.D., Ravindra Majeti, M.D., Ph.D., Irving L. Weissman, M.D., Chris H. Takimoto, M.D., Ph.D., Mark P. Chao, M.D., Ph.D., and Sonali M. Smith, M.D.

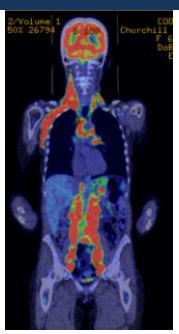
Table 1. Characteristics of the 22 Patients Who Were Treated.*

Characteristic	All Patients (N=22)	Patients with DLBCL (N=15)	Patients with Follicular Lymphoma (N=7)
Median age (range) — yr	59 (44–82)	60 (44–82)	59 (44–75)
Sex — no. (%)			
Male	12 (55)	7 (47)	5 (71)
Female	10 (45)	8 (53)	2 (29)
Median no. of previous therapies (range)	4 (2–10)	4 (2–10)	4 (2–9)
ECOG performance-status score — no. (%)†			
0	7 (32)	3 (20)	4 (57)
1	14 (64)	11 (73)	3 (43)
2	1 (5)	1 (7)	0
Lugano stage at diagnosis — no. (%)‡			
I or II	4 (18)	3 (20)	1 (14)
III or IV	15 (68)	11 (73)	4 (57)
Unknown	3 (14)	1 (7)	2 (29)
Disease refractory to previous rituximab regimen — no. (%)	21 (95)	14 (93)	7 (100)
Disease refractory to most recent regimen — no. (%)	14 (64)	9 (60)	5 (71)
Previous autologous stem-cell transplantation — no. (%)	4 (18)	2 (13)	2 (29)
5F9 maintenance dose level — no. (%)			
10 mg/kg	3 (14)	2 (13)	1 (14)
20 mg/kg	6 (27)	6 (40)	0
30 mg/kg	13 (59)	7 (47)	6 (86)

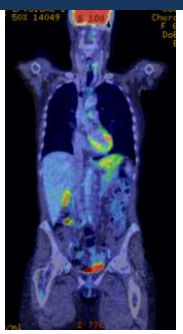
Table 2. Clinical Responses to Combination Therapy with 5F9 and Rituximab.*

Response	All Patients (N=22)	Patients with DLBCL (N=15)	Patients with Follicular Lymphoma (N=7)
Objective response	11 (50)	6 (40)	5 (71)
Complete response	8 (36)	5 (33)	3 (43)
Partial response	3 (14)	1 (7)	2 (29)
Stable disease	3 (14)	3 (20)	0
Progressive disease	8 (36)	6 (40)	2 (29)
Disease control	14 (64)	9 (60)	5 (71)

* Objective response was defined as a complete or partial response. Disease control was defined as a complete response, partial response, or stable disease.

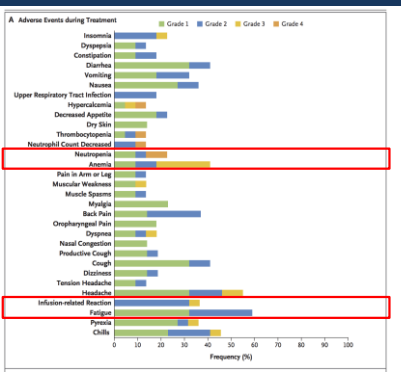


Baseline



Post C2

Risks



- At a median follow-up of 6.2 months among patients with DLBCL and 8.1 months among those with follicular lymphoma, 91% of the responses were ongoing.

However this is just one trial

Overall?

Original Research

Trends in the characteristics, dose-limiting toxicities and efficacy of phase I oncology trials: The Cancer Research UK experience

Han Hsi Wong [a,b,*], Claire Barton [a], Gary Acton [a], Robert McLeod [a], Sarah Halford [a]

[a] Cancer Research UK Centre for Drug Development, Angel Building, 407 St. John Street, London EC1V 4AD, UK
[b] Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Box 193, Cambridge Biomedical Campus, Hills Road, Cambridge CB2 0QQ, UK

Received 21 February 2016; received in revised form 28 June 2016; accepted 4 July 2016
Available online 8 August 2016

	No. of trials	
	1995–2003 (n = 24)	2004–2013 (n = 25)
No. of study centres:		
- 1	12	5
- 2	8	10
- 3	3	4
- >4	1	6
ECOG performance status eligibility:		
- 0–1	4	17
- 0–2	20	8
Tumour type:		
- Any solid	15	14
- Specific	9	11
Specific molecular target in tumour required	4	6
Line of treatment (excluding trials of imaging agent):		
- First/any	1	4
- Second or subsequent	22	20
Tumour biopsy:		
- Mandatory for all	2	2
- Mandatory for expansion cohorts	1	5
- Optional	9	9
Dose escalation method:		
- '3 + 3' or equivalent design	13	11
- Accelerated titration design	9	6
- Pharmacologically guided dose escalation	2	2
- Rolling six design	0	3
- Adaptive design	0	1
- None	0	2
Disease-specific expansion cohorts after MTD	1	2

	No. of trials	
	1995–2003 (n = 24)	2004–2013 (n = 25)
Type of agent (no. of patients):		
a) Single-agent study		
- Antiangiogenic	4 (99)	3 (95)
- Antibody (±drug conjugate)[a]	2 (25)	1 (29)
- Antisense oligonucleotide	0	1 (38)
- Cytotoxic (including prodrug)	8 (197)	3 (98)
- Imaging agent	1 (34)	1 (8)
- Inhibitor of protein or signalling pathway	4 (98)	7 (259)
- Radiosensitiser	0 (0)	1 (10)
- T-cell therapy	0 (0)	1 (14)
- Vaccine	1 (25)	2 (72)
b) Combination study		
- Antiangiogenic in combination with another agent[b]	0 (0)	2 (51)
- Cytotoxic in combination with another agent[c]	4 (125)	3 (76)
Route of administration:		
- Intravesical	1	0
- Parenteral	22	18
- Oral	1	7

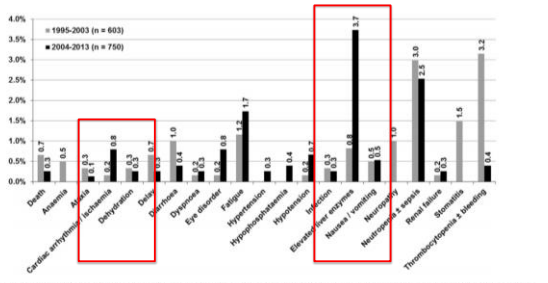


Fig. 1. Incidence of dose-limiting toxicities. Figures indicate the percentage of patients in the early or late trial groups who experienced DLTs. Only events with a frequency of ≥0.3% are shown.

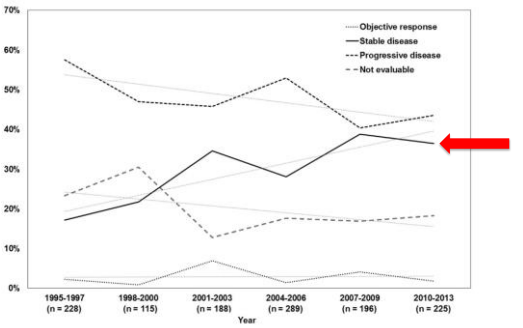
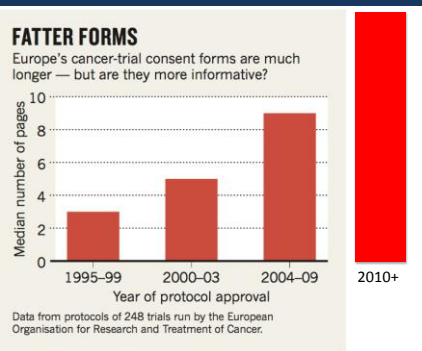


Fig. 2. Trends in best radiological response rates.

The most important question

What does this mean for sufferers?

What are they consenting for?



The therapeutic misconception

Patients entering early phase clinical trials often operate under what has been termed the therapeutic misconception, the ***mistaken*** notion that the purpose of the trial is to benefit them as individual patients, when, in fact, the primary study objective is to determine the dose and safety of a novel agent.

- Therapeutic ***misestimation***
  - Unknowingly ignore the facts
- Therapeutic ***optimism***
  - Knowingly ignore the facts

Original Article

The Culture of Faith and Hope

Patients' Justifications for Their High Estimations of Expected Therapeutic Benefit When Enrolling in Early Phase Oncology Trials

Daniel P. Sulmasy, MD, PhD[1]; Alan B. Astrow, MD[2]; M. Kai He, PhD[3]; Damon M. Seils, MA[4]; Neal J. Meropol, MD[5]; Ellyn Micco, MS[6]; and Kevin P. Weinfurt, PhD[4,7]

- Interviewed 45 patients enrolled in phase 1 or 2 oncology trials about their expectations of therapeutic benefit and their reasons for those expectations.
- Used a phenomenological, qualitative approach with 1 primary coder to identify emergent themes, verified by 2 independent coders

Questions

- ‘‘Out of 100 patients who participate in this study, how many on average will have their cancer controlled as a result of the therapy?’’ (Response options: 0-100 patients)
  - PROBE: What does it mean to be participating in a study of a new experimental therapy?
  - PROBE: What does ‘‘have their cancer controlled’’ mean to you?
  - PROBE: What does ‘‘on average’’ mean?

Questions

- How confident are you that the experimental therapy will control your cancer?’’ (Response options: 0-100%)1.
  - 1. Pretend that you are helping someone else to answer this question, and the person is not sure they understand the question. To help the person understand, can you rephrase this question in your own words?
  - 2. Does this mean the same thing to you as the first question I showed you?
    - [If yes] So for you, this [confidence question] is just another way of asking this [frequency question]?
    - [If no] How are these 2 questions different?
    - 3. What would your answer be to this [confidence] question?

Hope and Optimism

- Almost all participants, at least indirectly, made reference to hope or optimism in justifying their responses to queries about the meaning of their numerical expressions regarding expected therapeutic benefit

Reasons?

- Optimism as a performative expression
- Entering the trial as part of a battle with cancer
- Faith, whether in God, medicine or both

Optimism as a performative expression

- That is, they believed that by thinking optimistic thoughts and expressing this optimism to others they would actually positively influence the likelihood of experiencing individual benefit

Battle

- Even when facing a limited prognosis, many viewed their expressions of high expected therapeutic benefit as signs they were not quitters, would always continue the battle, and would never lose hope.

Faith

- Their faith expressions were of 2 types:
  - Faith in a religious sense
  - Faith in medicine.
  - Expressions of faith in individual physicians or in the medical profession or in science were far more common than overtly religious expressions of faith.

Conforming to social expectations of optimism

- The model patient
- Described their expressions of faith and optimism regarding the personal therapeutic benefit they expected from the trial in a way that suggested they were conforming to social expectations of how they should behave

Optimism despite realism

- Almost all patients (42 of 45) reported a basic understanding that the reason the trial was being performed was because the true therapeutic benefit to be expected in a population of cancer patients receiving the study drug was unknown.
- They frequently, however, distinguished this realism about the trial, from what they expected would happen to them

Altruism

- Although it was rarely the primary reason participants gave for enrolling, most participants (30 of 45) spontaneously expressed an altruistic motivation when asked about their beliefs and expectations about the trial.

Ethical implications

- Most patients were NOT confused about the nature of their early phase study
- Classic misconceptions challenged:
  - Failure of adequate disclosure by the investigator
  - Failure of adequate comprehension
- **Simply expressing faith and optimism**

Ethical implications

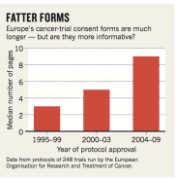
- The belief that personal will can effect a change in the course of bodily disease, the conflation of hope and optimism, and the notion that the medical system embodies and defines the limits of hope are all constructs of a particular historical moment in our particular culture.

Ethical implications

- BENEFIT
  - Psychological defense mechanism
- RISK
  - Cognitive bias
  - Vulnerable to coercion

Challenges

- Consent – ?appropriate format
  - Increasing number of early phase trials
  - Increasing number 'immune' side effects
  - Biomarker driven design
  - Accounting for therapeutic misconception



"I think there's always that hope that by participating you'll hopefully help yourself and help others."

Summary

- Early phase trials are focused on the effects of the drug not the effectiveness of the drug
- Increasing number of trials involving biomarkers and immune therapies
- Overall we do not appear to be increasing the cure rate*
- Risks versus benefits (individual)
- Most patients Acknowledge: facts & maintain faith and optimism
- Protect vulnerable patients
- Consent should not be a single time point