

The clinical trials we want!

- How to find, select and shape trials that are actually good for your patients.
- Beware fake news- false beliefs others want you to fall for and essential information they omit.

Bettina Ryll MPNE

Overview of the session

- Why clinical trial matters
- How to find clinical trials
- How to select clinical trials
- How to shape clinical trials

Expectation management wrt clinical trials

Patient advocates are traditionally expected to

- fundraise for clinical research
 - advertise for clinical trials
 - recruit for clinical trials
 - not to challenge the system
 - focus on traditional topics
-
- be grateful

Patient voice



FEET

MPNE

Pet Hate # 200 - Moral High Horses

I think drugs
are terrible.

Man, I'm just a high
horse - not a morally
high one.



Arita

A patient perspective

- **How to use clinical trials to improve your chances to survive**
- **How to make sure that patients only have good trials to choose from**

Patients are an own stakeholder group with overlapping and non-overlapping interests with any other stakeholder group.

Science matters

- There will always be patients with advanced cancer.
- Medical progress depends on scientific progress.

but

- Not all Science is good.
- And not every human price is justifiable.

**Just because it's called 'Science'
doesn't mean it's good let alone ethical.**



Known officially as the Tuskegee Study of Untreated Syphilis in the Negro Male, the study began at a time when there was no known treatment for the disease.



<https://www.history.com/news/the-infamous-40-year-tuskegee-study>

Know your rights- the Helsinki Declaration

Patient interest FIRST.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health,

Free to join, free to leave.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.



The screenshot shows the official website for the WMA Declaration of Helsinki. At the top, there is a navigation menu with links for 'WHAT WE DO', 'POLICY', 'PUBLICATIONS', 'NEWS & PRESS', 'WHO WE ARE', 'JUNIOR DOCTORS', and 'MEMBERS AREA'. Below the navigation is a search bar and social media icons. The main heading reads 'WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS'. A list of dates and locations where the declaration was adopted is provided, including Helsinki (1964), Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West (1996), Edinburgh (2000), Washington DC (2002), Tokyo (2004), Seoul (2008), and Fortaleza (2013). A 'Preamble' section is visible, starting with 'The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects...'. On the right side, there are sections for 'Policy Types', 'Archived Versions' (listing various dates from 1964 to 2008), 'Tags' (listing categories like Clinical Study, Ethics, etc.), and 'Other Posts'. At the bottom, a URL is provided: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>

Know your traditions- why you should care about a guy who lost his head.

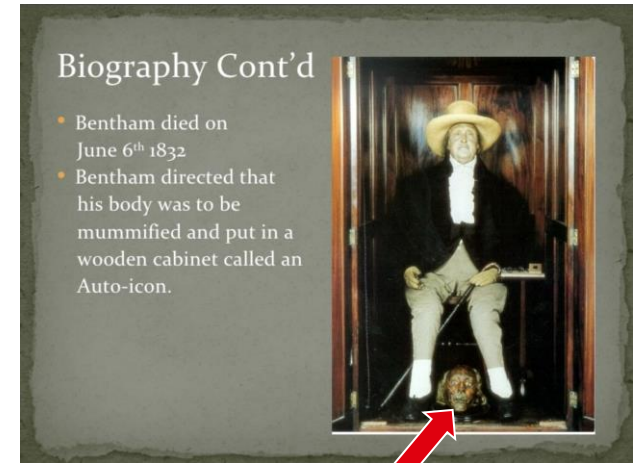
Individual versus utilitarian traditions- 'is it ok to sacrifice the individual for the 'greater good' of society?'

≠ Helsinki declaration: clearly individualistic perspective.

People will argue what is convenient for them.

Know where you stand.

A solution has to take BOTH the individual as well as the societal perspective into account.

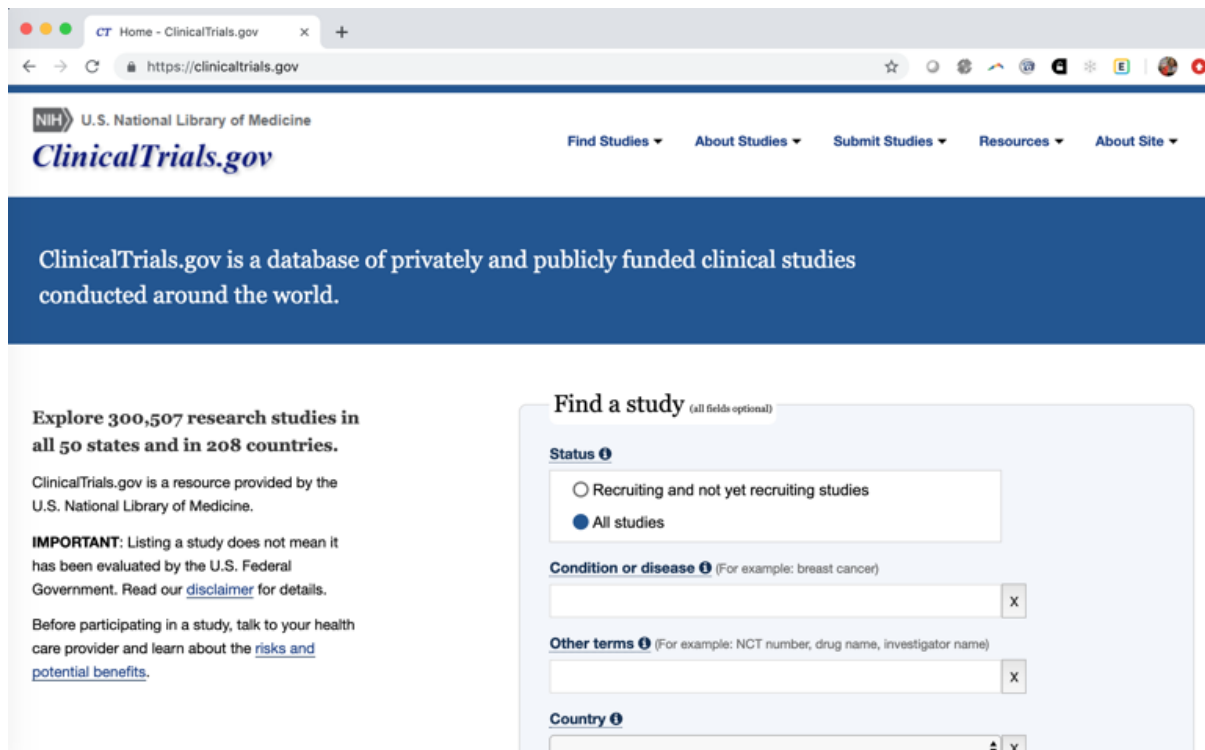


<https://www.slideshare.net/alannamlawson/jeremy-bentham-13121787>

How to find clinical trials- important to know

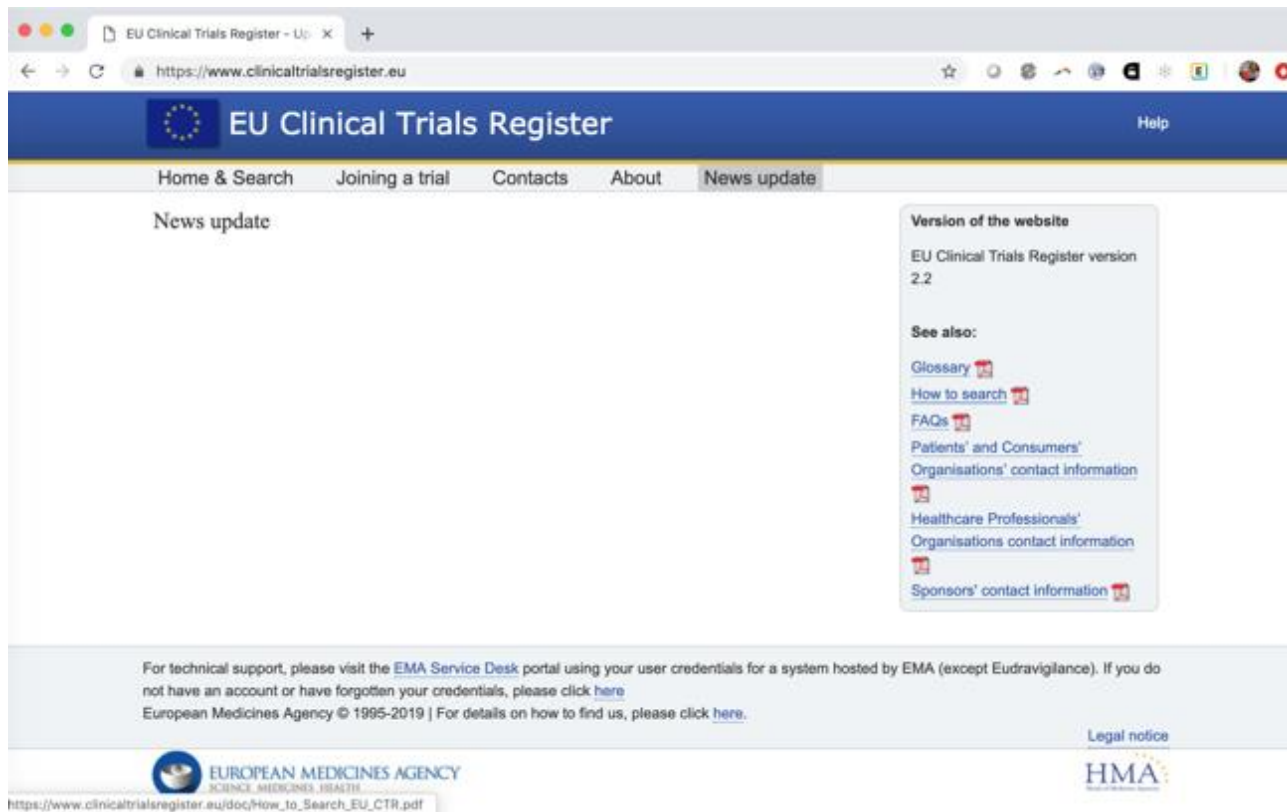
- Clinical trials need to be registered - find that database
- Avoid biased databases- e.g. maintained by single sponsors
- Beware financial motivations for matching patients to trials
- Be aware of filters and biased search algorithms- e.g. geographical, indications ('Melanoma' vs 'solid tumour')

US- Clinicaltrials.gov



The screenshot shows the ClinicalTrials.gov website interface. At the top, there is a navigation bar with the NIH logo and the text "U.S. National Library of Medicine" and "ClinicalTrials.gov". To the right of the logo are several menu items: "Find Studies", "About Studies", "Submit Studies", "Resources", and "About Site". Below the navigation bar is a blue banner with the text: "ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world." Below the banner, on the left, is a section titled "Explore 300,507 research studies in all 50 states and in 208 countries." followed by a paragraph: "ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine." and an "IMPORTANT" notice: "Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our [disclaimer](#) for details." Below this is another paragraph: "Before participating in a study, talk to your health care provider and learn about the [risks and potential benefits](#)." On the right side of the page is a "Find a study" search form with the subtitle "(all fields optional)". The form contains several fields: "Status" with radio buttons for "Recruiting and not yet recruiting studies" and "All studies" (selected); "Condition or disease" with a text input field and a clear button (X); "Other terms" with a text input field and a clear button (X); and "Country" with a dropdown menu and a clear button (X).

Europe- EUCTR





The screenshot shows the EU Clinical Trials Register website in a browser. The browser's address bar displays the URL <https://www.clinicaltrialsregister.eu>. The website's header features the European Union flag and the text "EU Clinical Trials Register" with a "Help" link. A navigation menu includes "Home & Search", "Joining a trial", "Contacts", "About", and "News update". The main content area is titled "News update" and is currently empty. On the right side, there is a sidebar with the following sections:

- Version of the website**
EU Clinical Trials Register version 2.2
- See also:**
 - [Glossary](#)
 - [How to search](#)
 - [FAQs](#)
 - [Patients' and Consumers' Organisations' contact information](#)
 - [Healthcare Professionals' Organisations contact information](#)
 - [Sponsors' contact information](#)

At the bottom of the page, there is a footer with the following text: "For technical support, please visit the [EMA Service Desk](#) portal using your user credentials for a system hosted by EMA (except Eudravigilance). If you do not have an account or have forgotten your credentials, please click [here](#). European Medicines Agency © 1995-2019 | For details on how to find us, please click [here](#)." The footer also includes the European Medicines Agency logo and the text "SCIENCE. MEDICINES. HEALTH.", the HMA logo, and a link to "Legal notice". The URL https://www.clinicaltrialsregister.eu/doc/how_to_Search_EU_CTR.pdf is visible at the bottom left of the page.

← → ↻ Not Secure | apps.who.int/trialsearch/ ☆ 🔍 🌐 🌈 🌐 🌐 🌐 🌐 🌐 🌐 🌐 🌐

 World Health Organization

 International Clinical Trials Registry Platform Search Portal

Home Advanced Search List By ▶ Search Tips UTN ▶ ICTRP website ▶ REGTRAC Contact us

Search Search tips

Search for [clinical trials in children](#)

Without Synonyms

Phases are

- All
- Phase 0
- Phase 1
- Phase 2
- Phase 3
- Phase 4

With results only

Rare diseases / orphan drugs

Welcome

- The Clinical Trials Search Portal provides access to a central database containing the trial registration data sets provided by the registries listed on the right. It also provides links to the full original records.
- To facilitate the unique identification of trials, the Search Portal bridges (groups together) multiple records about the same trial. [More information](#)
- Please note: This Search Portal is not a clinical trials registry. [How to register a trial](#)
- It is now possible to export the results of the search into XML. [More information](#)
- Crawling the ICTRP database now requires a username/password. To request access to the crawling pages please send an email to ictinfo@who.int ([This service is now enabled](#))
- A new field called 'Prospective registration' has been added to the ICTRP database, More details about this new field can be found [here](#)
- The WHO Database of Regulatory Information Tracking of Clinical Trials Registration & Ethics Committees (REGTRAC) is now online [here](#)

Data Providers

Data sets from [data providers](#) are updated every Friday evening according to the following schedule:

Every week:

- Australian New Zealand Clinical Trials Registry, last data file imported on **11 February 2019**
- Chinese Clinical Trial Registry, last data file imported on **26 June 2019**
- ClinicalTrials.gov, last data file imported on **24 June 2019**
- EU Clinical Trials Register (EU-CTR), last data file imported on **14 January 2019**
- ISRCTN, last data file imported on **26 June 2019**
- The Netherlands National Trial Register, last data file imported on **26 June 2019**

Every 4 weeks:

- Brazilian Clinical Trials Registry (ReBec), last data file imported on **15 January 2019**

Trial record 5 of 27 for: bms | Recruiting Studies | Melanoma

[Previous Study](#) | [Return to List](#) | [Next Study](#)

A Study of NKTR-214 Combined With Nivolumab vs Nivolumab Alone in Participants With Previously Untreated Inoperable or Metastatic Melanoma



**BUT
beware incomplete,
inconsistent or fraudulent
information**

ClinicalTrials.gov Identifier: NCT03635983

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

Recruitment Status: Recruiting
 First Posted: August 17, 2018
 Last Update Posted: June 19, 2019
[See Contacts and Locations](#)

Arms and Interventions

Go to

Sponsor:
Bristol-Myers Squibb

Collaborator:
Nektar Therapeutics

Information provided by (Responsible Party):
Bristol-Myers Squibb

Arm	Intervention/treatment
Experimental: Combination NKTR-214 + Nivolumab	Biological: NKTR-214 Specified dose on specified days Other Names: <ul style="list-style-type: none"> Rempegaldesleukin BMS-986321
Experimental: Monotherapy Nivolumab	Biological: Nivolumab Specified dose on specified days Other Names: <ul style="list-style-type: none"> Opdivo BMS-936558

'The difference between medicine and poison is the dose'

How to select clinical trials- important to know

- **Understand your motivation**
- **Understand the underlying Science**

How to select clinical trials- what's the motivation?

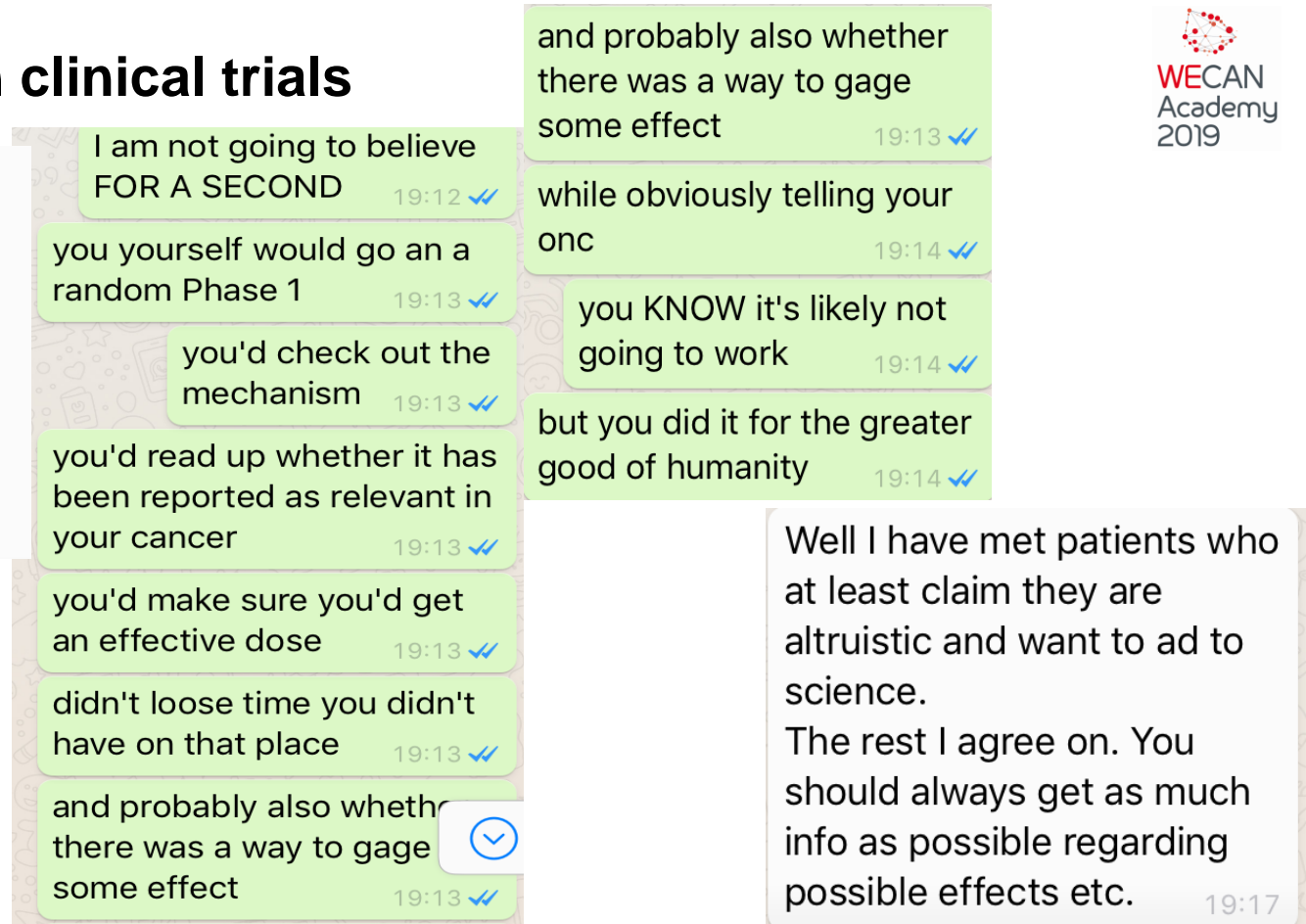
- **Is it a clinical trial you are looking for?**
- **Why are you looking for a clinical trial?**
- Standard of care insufficient
- All lines of therapy exhausted
- Drugs not reimbursed
- ?

- **Treatment option**
- **Access**

Why patients join clinical trials

Than again, I believe that you should never enter a phase I trial and expect a benefit but with the aim to help (hopefully) future patient who might have a benefit in future trials or from approved treatment.

different rules for different people



I am not going to believe FOR A SECOND 19:12 ✓

you yourself would go an a random Phase 1 19:13 ✓

you'd check out the mechanism 19:13 ✓

you'd read up whether it has been reported as relevant in your cancer 19:13 ✓

you'd make sure you'd get an effective dose 19:13 ✓

didn't loose time you didn't have on that place 19:13 ✓

and probably also whether there was a way to gage some effect 19:13 ✓

and probably also whether there was a way to gage some effect 19:13 ✓

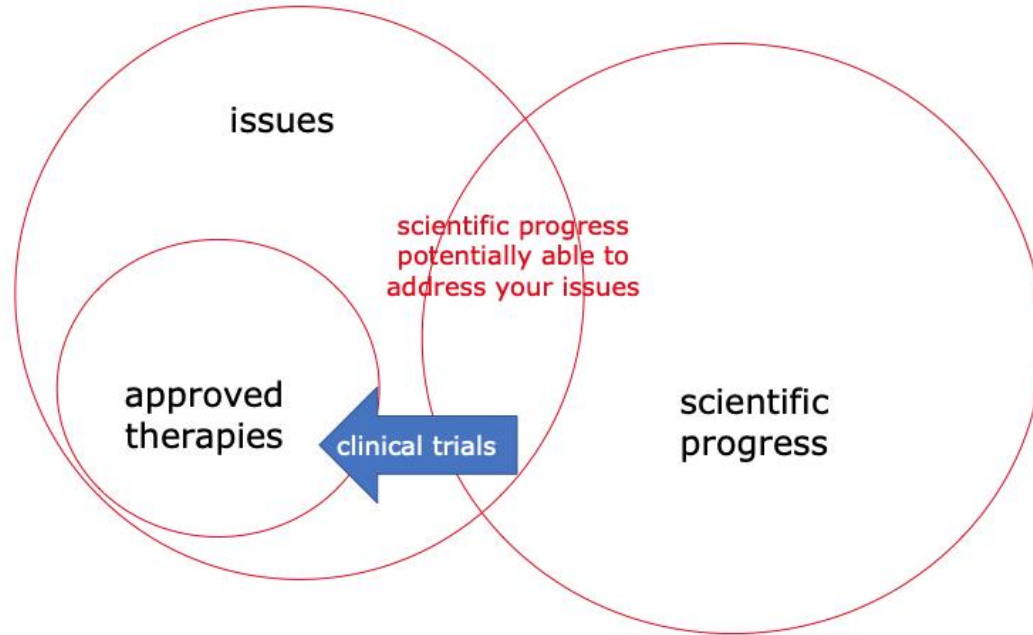
while obviously telling your onc 19:14 ✓

you KNOW it's likely not going to work 19:14 ✓

but you did it for the greater good of humanity 19:14 ✓

Well I have met patients who at least claim they are altruistic and want to ad to science.
The rest I agree on. You should always get as much info as possible regarding possible effects etc. 19:17

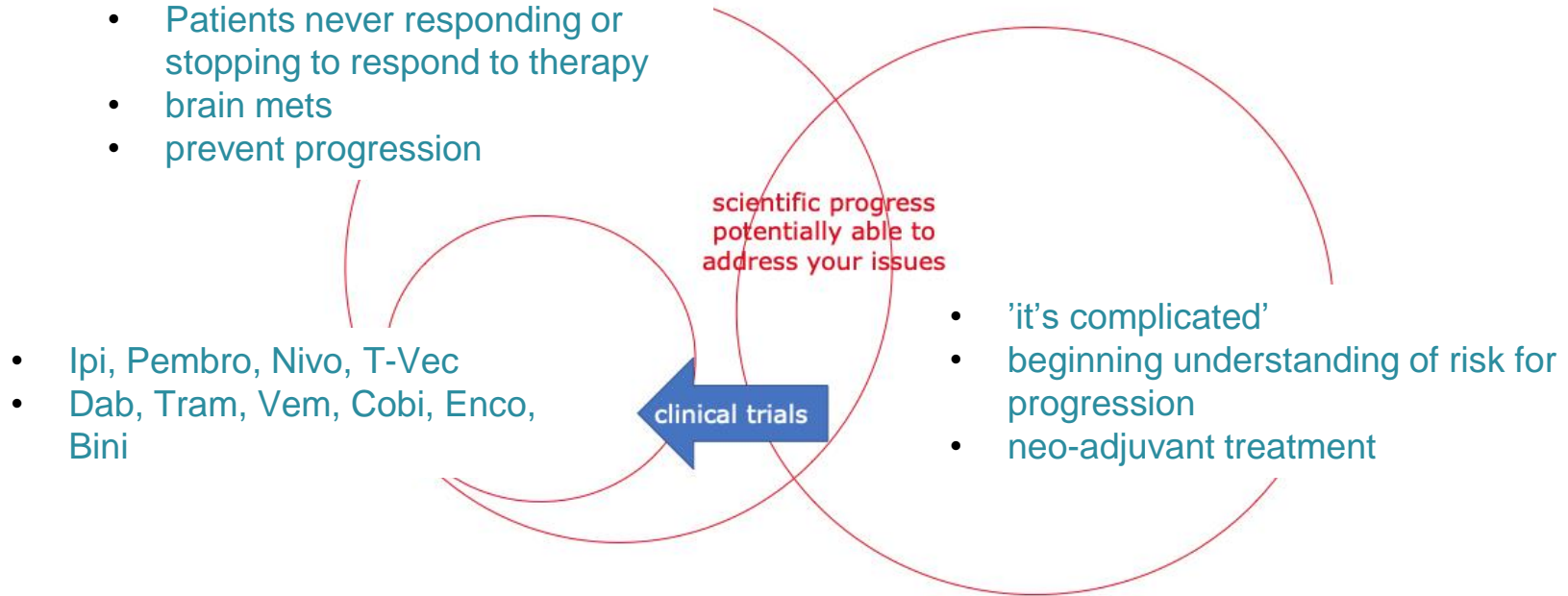
Know your treatment and scientific landscape



Follow Scientific news

- Pubmed- biomedical publications
- Google scholar
- Subscription services: <https://ecancer.org/>, ASCO, ESMO, NEJM, Lancet
- Google alerts, Google scholar alerts
- Medical journals directly- always something one misses
- Attend scientific meetings

Know your treatment and scientific landscape



How to **choose** a clinical trial

Clinical trial elements to watch out for

- what do you know about the drug?
- randomisation
- placebo
- blinding
- cross-over

Uneven randomisation, blinding, early interim analyses, cross-over, in particular when uni-directional: expect one arm to perform considerably better than the other.

CTC- How to choose when you are the patient

- Choose a design where you get the drug you want: EAP? Phase 2 after a good Phase 1?
- Avoid placebo/ nocibo because you cannot recover time lost in useless therapies
- If that's not possible, find at least a trial with cross-over

Shaping clinical trial design

Why care about clinical trial design?



- Earliest access to new medicines
- New doesn't mean better- mind your risk mitigation strategy
- Trials are designed to answer population-based questions. We are individuals.
- Rules and methods evolve constantly- they are NOT set in stone.

Understand the clinical trial ecosystem- everyone has vested interests

- Pharmaceutical Industry- financial
- Regulators – SAFETY, efficacy
- HTA and payors- financial, social justice
- Clinicians and hospitals- financial, publications, careers
- NYDs (not-yet-diagnosed)- financial, sense of security

'There is no group of angels'
Anna Wagstaff, WECAN 2019



Pet Hate # 200 - Moral High Horses

I think drugs
are terrible.

Man, I'm just a high
horse - not a morally
high one.



Arita

My personal baseline assumptions- (only) slightly exaggerated.

- Clinicians don't understand statistics, unconventional data sources nor HTA.
- Statisticians don't understand oncology.
- Pharma is risk-averse, it's always the regulator's fault, but you can count on financial motives.
- HTAs don't understand Molecular Biology.
- Payers are the real shadow eminence.
- Everyone has vested interests.
- Everyone blames the person that is NOT in the room.
- **There are outliers in every place.**
- No one has money. Academics have less money than Pharma.
- No one has time. Pharma has less time than Academics.
- People design trials for OTHERS, not for themselves.
- **Patients are upsetting the current system.**
- **Patients aren't here to die on clinical trials.**
- **Clinical trials that don't recruit get amended.**

Do we need more clinical trials?

Numbers of trials using common combo strategies:

1. Anti-CTLA-4 agents: 251
2. Chemotherapies: 170
3. Radiotherapies: 64
4. Anti-VEGFA agents: 43
5. Chemoradiotherapy combos: 42

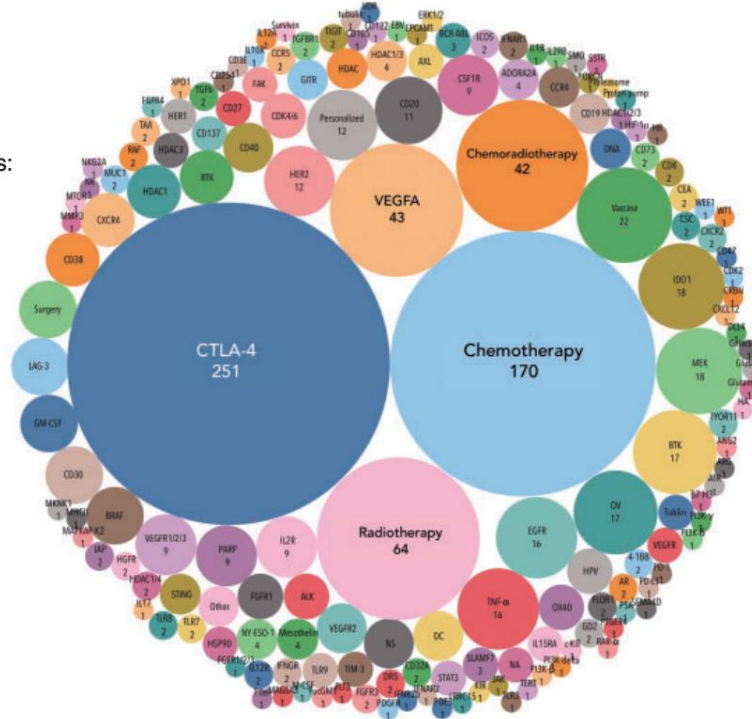


Figure 7. The landscape analysis of targets of anti-PD-1/L1 combination trials. The size of the bubble correlates to the number of trials.

<https://www.ncbi.nlm.nih.gov/pubmed/29228097>

2018

So unless you already got a side-effect free cure for your cancer, research always answers what your patients need and want and your patients are queuing to join clinical trials...



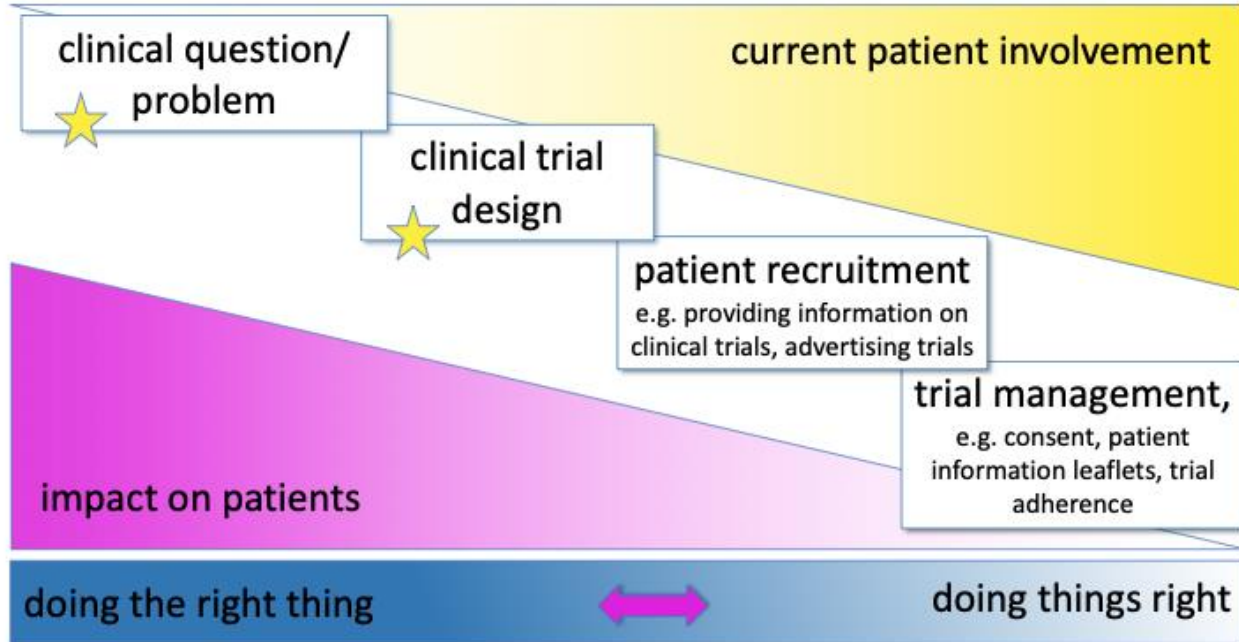
The definition of insanity is doing the same thing over and over again and expecting a different result.

**Quality not Quantity.
We need BETTER trials.**

The strategy piece

Return on Engagement

Patient involvement in clinical trial design



<http://www.informed-scientist.org/presentation/the-role-of-patient-groups-in-the-clinical-trial-process>

B. RYLL

the real issues



Informed Consent



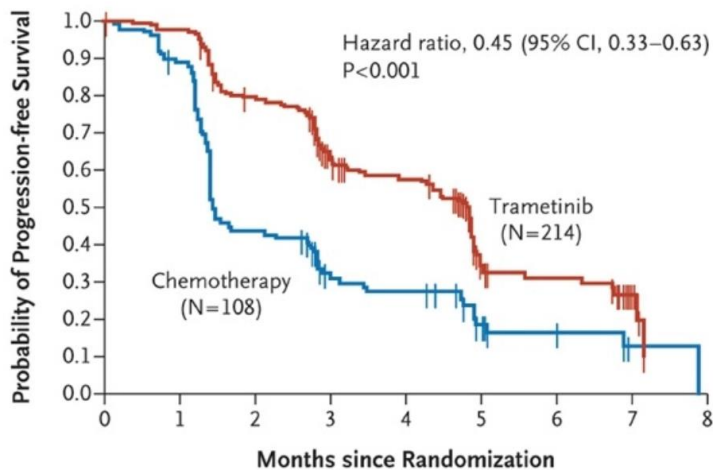
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B.Ryll, MD/PhD 5th July 2019

Some substance

Why I care

A Progression-free Survival

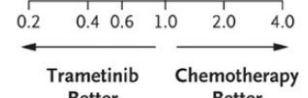


No. at Risk

	0	1	2	3	4	5	6	7	8
Chemotherapy	108	87	43	24	21	10	6	1	0
Trametinib	214	205	163	100	88	28	22	5	0

B Disease Progression or Death

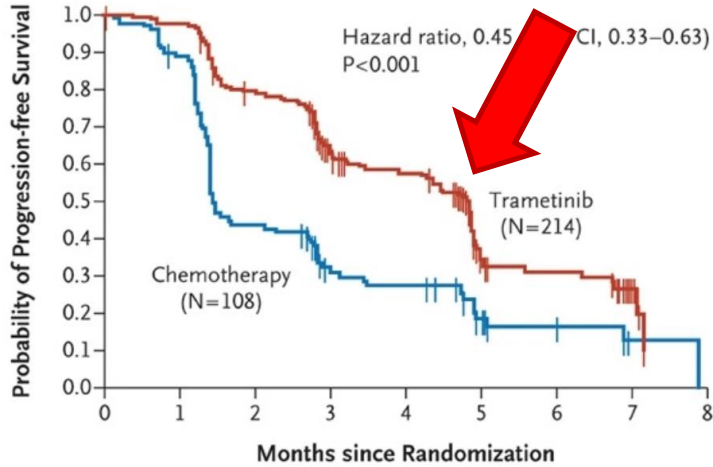
Subgroup	No. of Patients	Hazard Ratio (95% CI)
Intention-to-treat population	322	0.45 (0.33-0.63)
Mutation status		
V600E, no brain metastasis	273	0.44 (0.31-0.64)
V600E, no brain metastasis, and previous treatment	97	0.52 (0.29-0.93)
V600E, no brain metastasis, and no previous treatment	176	0.44 (0.28-0.69)
V600E	281	0.47 (0.33-0.67)
V600K	40	0.50 (0.18-1.35)
Age		
≥65 yr	71	0.58 (0.29-1.18)
<65 yr	251	0.44 (0.31-0.65)
Sex		
Male	173	0.53 (0.33-0.84)
Female	149	0.38 (0.23-0.62)
ECOG status		
0	205	0.55 (0.36-0.83)
1	117	0.38 (0.22-0.65)
Disease stage		
IIIc, IVM1a, IVM1b	114	0.44 (0.25-0.78)
IVM1c	207	0.43 (0.28-0.66)
Lactate dehydrogenase		
≤ULN	200	0.45 (0.29-0.71)
>ULN	119	0.47 (0.29-0.76)



<https://www.nejm.org/doi/full/10.1056/NEJMoa1203421>

Why I care

A Progression-free Survival



No. at Risk

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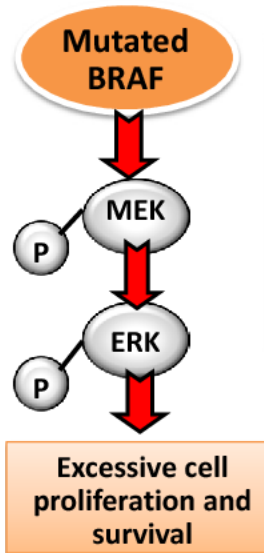
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0.2 0.4 0.6 1.0 2.0 4.0

Trametinib Better Chemotherapy Better

<https://www.nejm.org/doi/full/10.1056/NEJMoa1203421>

Scientific reasoning




- BRAFmut Melanoma depends on activated BRAF pathway
 - BRAF works better than DTIC
 - MEK works better than DTIC
 - BRAF works better than MEK
 - BRAF+ MEK works best
-
- We got 3 BRAF+ MEK combinations.
 - DTIC old standard of ~~care~~ desperation, dirt- cheap.
 - Which trial design would you want to see?
 - Which trial design do you think you will get?

What we got

- [Vem](#) vs DTIC 2011
- [Dab](#) vs DTIC 2012
- Tram vs DTIC 2012
- [Vem](#) + Cobi vs [Vem](#) + **placebo** 2014
- [Dab](#) + Tram vs [Vem](#) 2015
- [Enco](#) vs [Enco](#)+ Bini vs [Vem](#) 2018

- [BRAF inhibitors](#)
- [MEK inhibitors](#)



why do you think
they used a
placebo?



New Drugs Stir Debate on Rules of Clinical Trials

By AMY HARMON SEPT. 18, 2010



Two Cousins, Two Paths Thomas McLaughlin, left, was given a promising experimental drug to treat his lethal skin cancer in a medical trial; Brandon Ryan had to go without it.

Monica Almeida/The New York Times, left

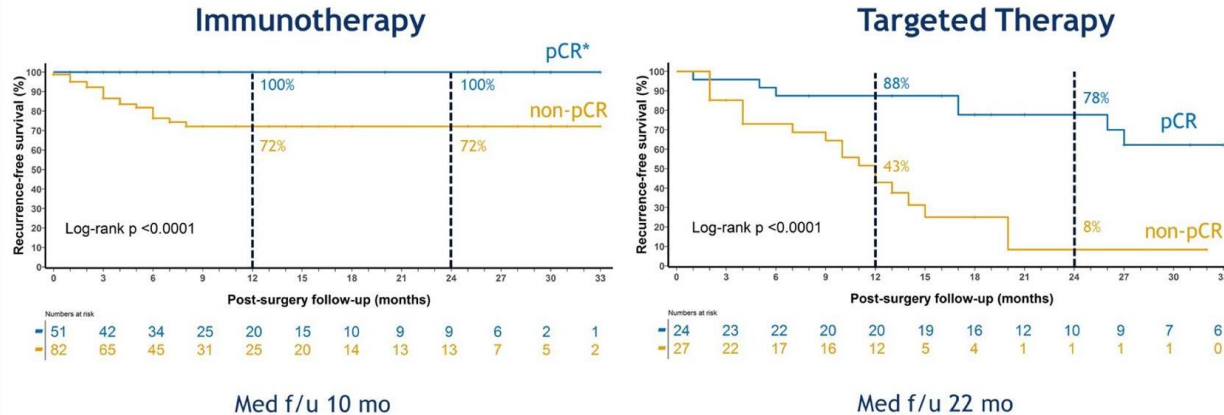
<https://www.nytimes.com/2010/09/19/health/research/19trial.html>

RELATED C



CONSULTS
Ask an F

RFS by pathological response and drug



PRESENTED AT: 2019 ASCO ANNUAL MEETING

#ASCO19
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PRESENTED BY: Alexander M Menzies, MIA

* 1 pt died from toxicity without recurrence, censored at time of death

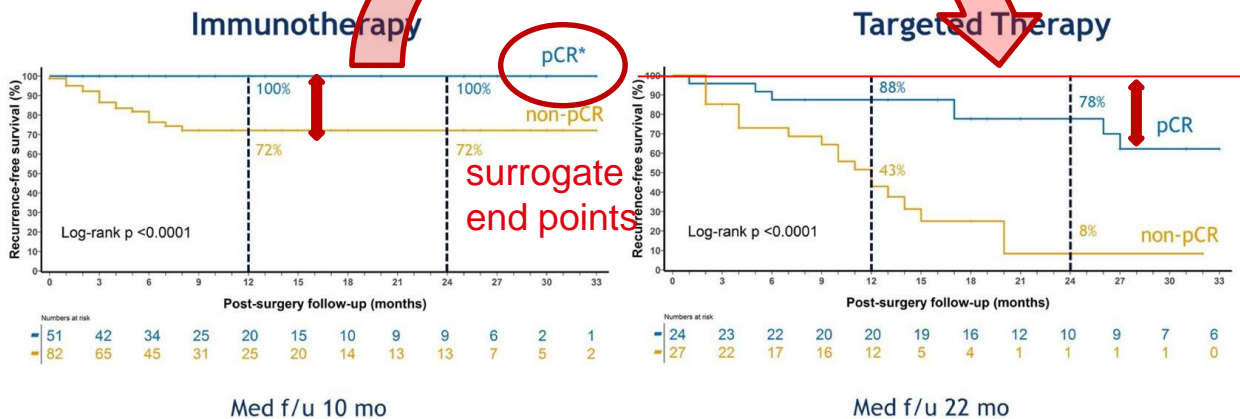


Presented By Alexander Menzies at 2019 ASCO Annual Meeting

RFS by pathological response and drug

mechanism

next trial design?



PRESENTED AT: 2019 ASCO ANNUAL MEETING

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* 1 pt died from toxicity without recurrence, censored at time of death



Presented By Alexander Menzies at 2019 ASCO Annual Meeting

The trials we don't want

Scientifically unsound.

Helsinki violations.

Inferior comparators.

Trial design not in patient's best interest.

Treatment effect large but still randomised.

You wouldn't go on this trial either!

MPNE

The trials we don't want

- S**cientifically unsound.
- H**elsinki violations, esp Art 8 and Art 26.
- I**nferior comparators.
- T**rial design not in patient's best interest.
- T**reatment effect large but still randomised.
- Y**ou wouldn't go on this trial either!

MPNE

Summary

- Clinical trials offer treatment options for patients who have no other option left
- If we want a better future for our patients, we need research
- Not all research is good- the normal distribution also applies here
- Finding, selecting and shaping research requires expertise
- Research takes time – favour long-term engagement and interaction with research groups and- no short-cut to knowledge.
- Know where to target your efforts
- Know your non-negotiables

Take home

- **Trials that don't recruit get amended.**
- **Don't support research you haven't read or that you don't understand.**

Thank you for listening

- bettina.ryll@mpneurope.org