How are we doing clinical trials for the last decades?

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Clinical Research in Rare Cancers
03/12/2017

There are different types of information in clinical research

Expert opinion

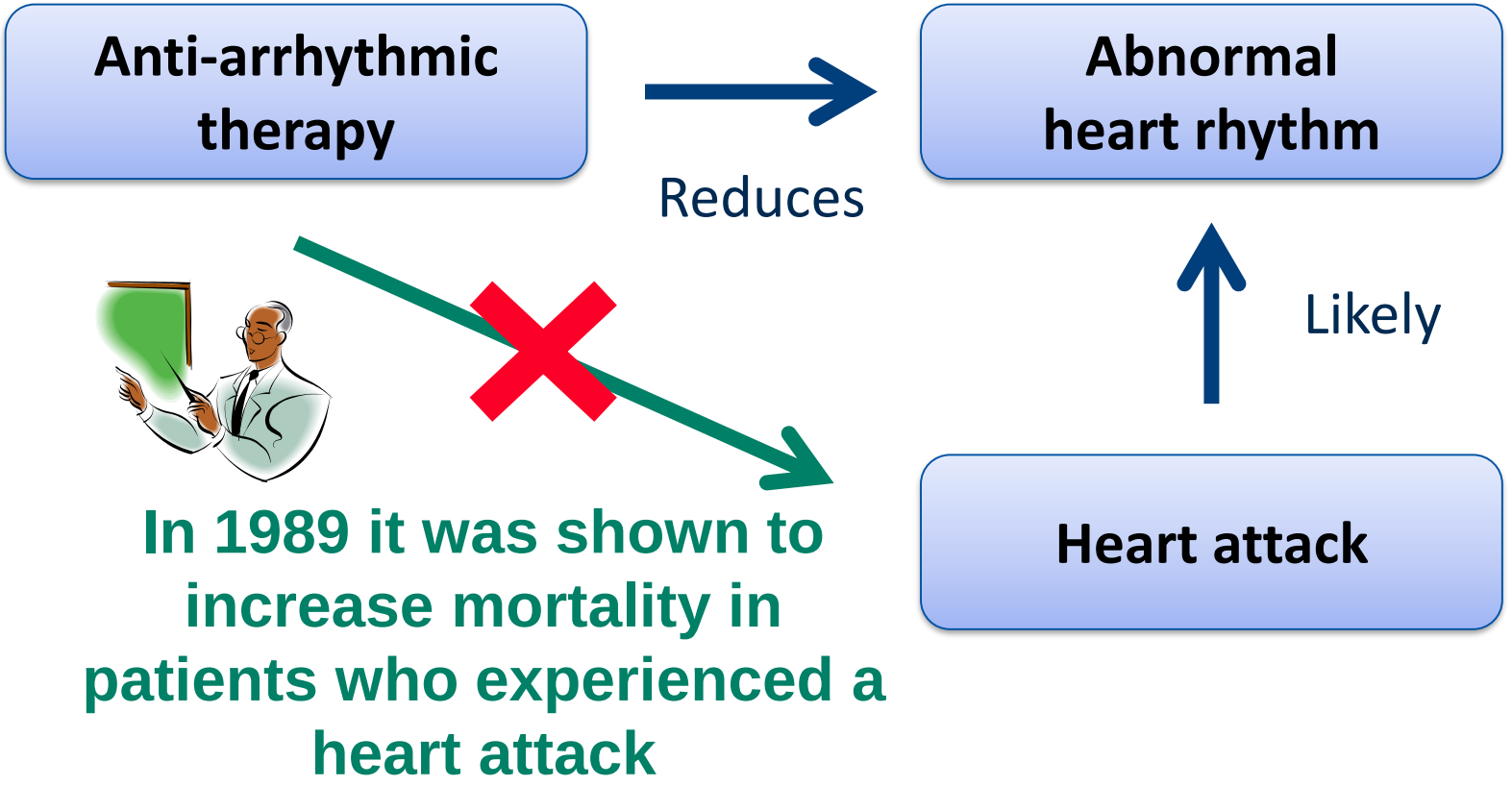
WonderPill®

- Experience
- Beliefs
- Intuition
- Deduction

But …

The case of anti-arrhythmic therapy

Timing: the 1980s



A study of one patient

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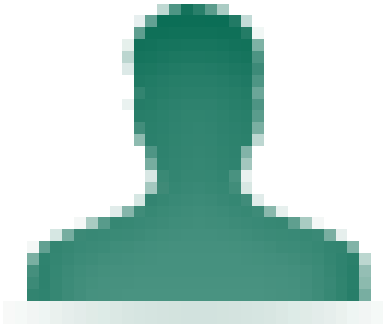

- Useful information on symptoms and response to treatment
- Sometimes the only information for rare diseases

But each patient is unique: are symptoms and/or response "unusual" or "normal"?

A series of patients

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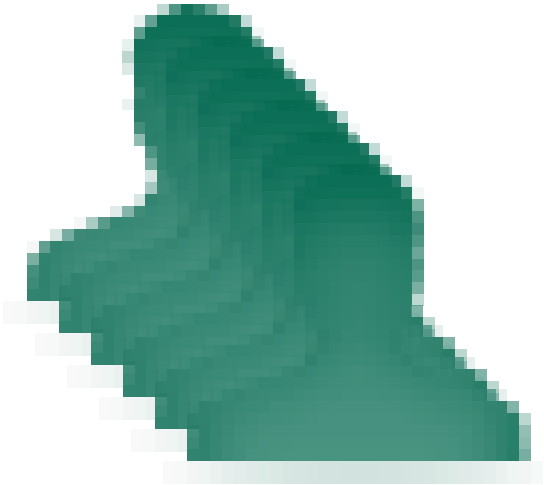


Retrospective:

All patients with an angiosarcoma treated with WonderPill® in the last 2 years in Istituto Nazionale dei Tumori

Can be obtained from

- hospital records
- registries
- existing trial databases

Retrospective series

- Information is already available
  - No “loss to follow-up”
  - Quick to complete
- Important for rare diseases
- Logistically very easy
- Not very expensive
  - One only needs to collect the information

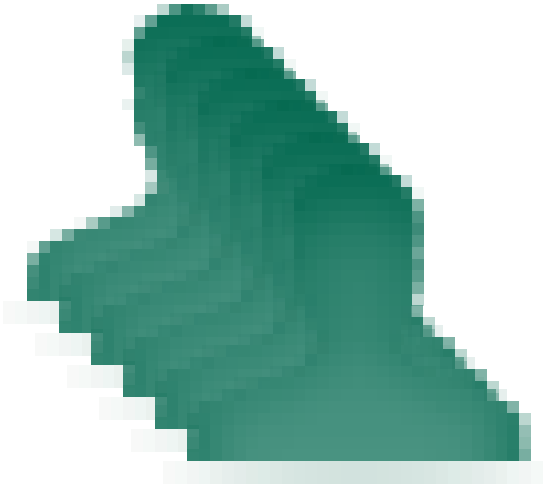
But …

- Relies on/limited to recorded data
- Time effect?
- May be very selected
  - E.g. treated by only one surgeon

  or very heterogenous
  - Different sources of data (e.g. from different hospitals)
  - No control over how treatment is given → standard practice
  - No control over how outcome is assessed
- Only for treatments already in use

A series of patients

WonderPill®



Prospective:

All patients with an angiosarcoma who will be treated with WonderPill® in the next 2 years

Can be organized as a

- registry, reflecting standard practice
- clinical trial where intervention is pre-specified

Prospective series

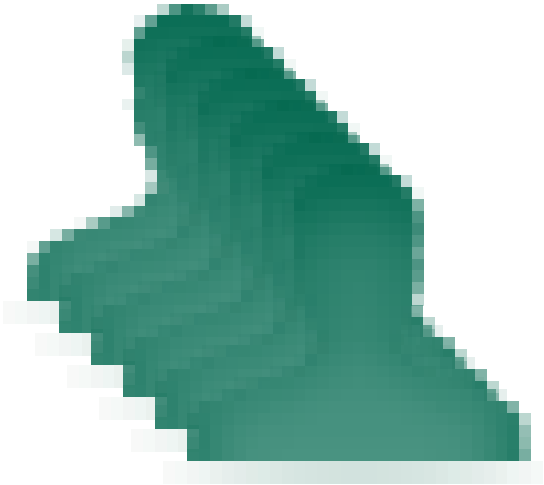
- Information to be collected is defined upfront
  - Which patients?
  - Which treatment / doses?
  - What follow-up?
  - Which parameters
- Very targeted research

But …

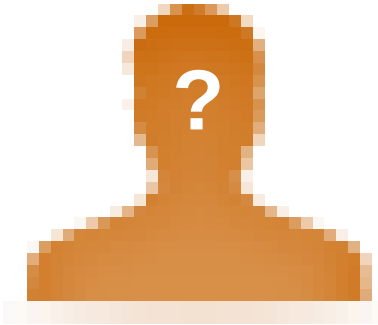
- Have to wait for the results
- May require approval from regulatory offices
- Expensive:
  - Treatment
  - Assessments
- Logistically more demanding
  - Central system for data collection
- May still represent a highly *selected* population

And …

WonderPill®



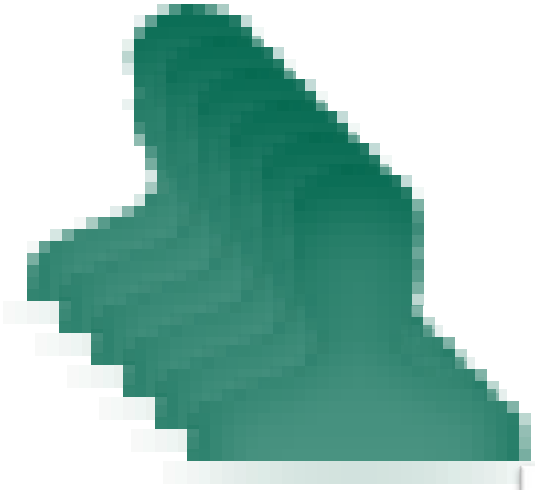
Standardicin®



Compare to a historical control

WonderPill®

Standardicin®



EUROPEAN JOURNAL OF CANCER 44 (2008) 2433–2436

available at www.sciencedirect.com

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journal homepage: www.ejconline.com

ELSEVIER

EJC

Standardicin in patients with advanced angiosarcomas of soft tissue: A retrospective study of the EORTC soft tissue and bone sarcoma group

EORTC

Compare to a historical control

- Information available
- Does not require additional patient commitment
  - thus also less expensive
- Could be more ethical if control (standard?) treatment is
  - believed to have little effect
  - and/or very toxic

But …

- Still applicable?
- Same patient population?
  - Same characteristics?
  - Same staging system?
  - …
- Same imaging / diagnostic tools for assessing outcome?

Compare to a matching control group

Overall survival

WonderPill®

Standardicin ®

Compare to a matching control group

- Can be done retrospectively but also prospectively
- Match patients so that differences of outcome between the two groups cannot be attributed to matching factors

But …

- No control over who gets which treatment
  - Not all “confounding” factors are as obvious as age!

A randomized clinical trial (RCT)

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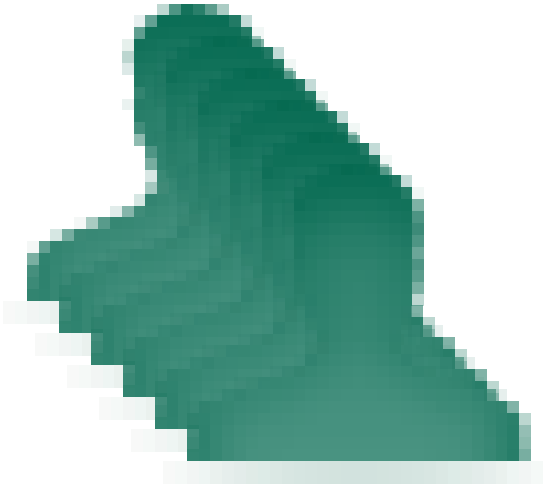
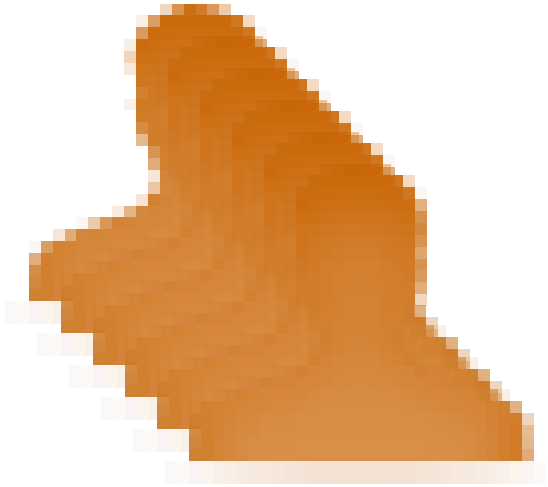




Patients are **randomly** assigned to receive one of two treatments

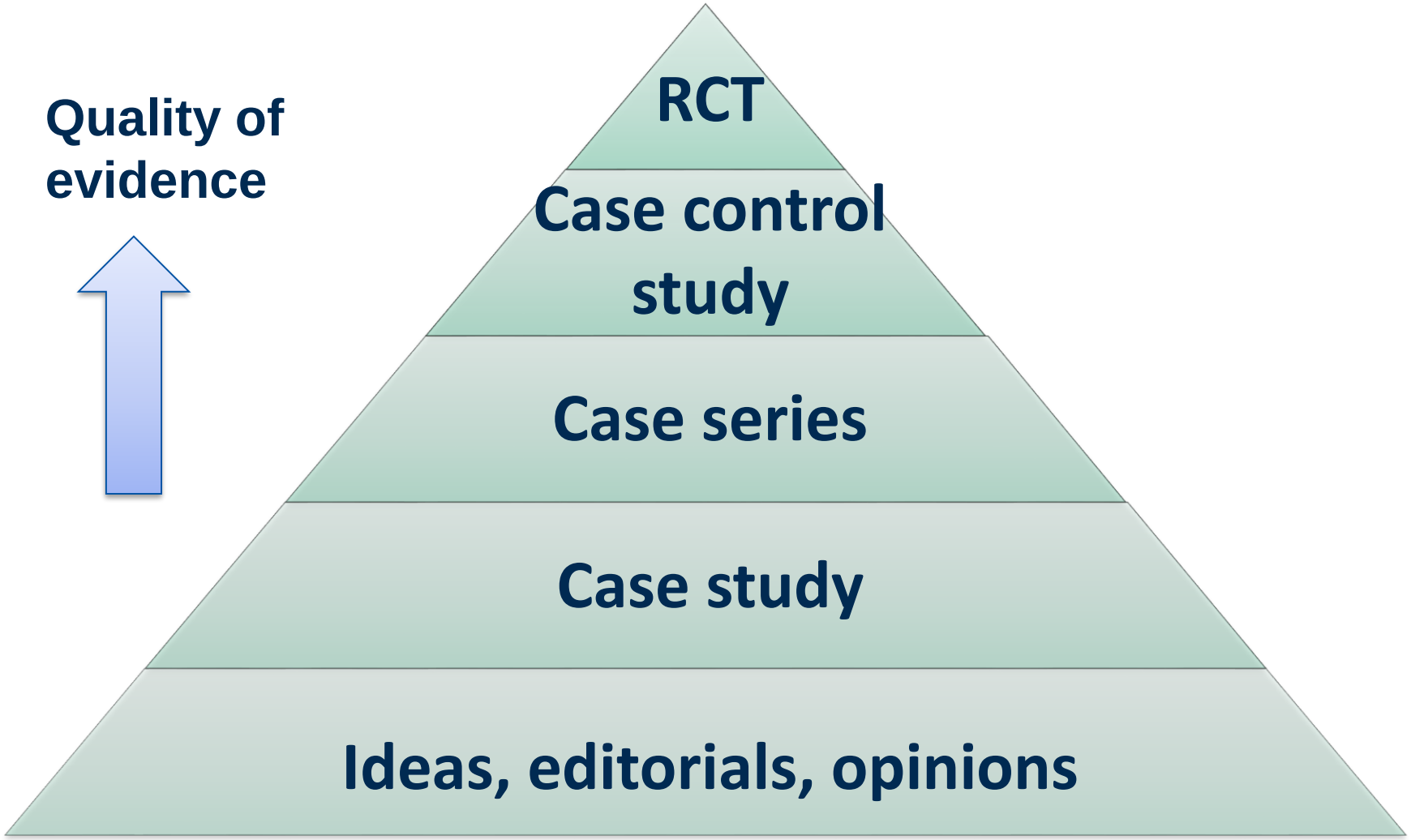
A randomized clinical trial (RCT)

- Ensures that the treatment arms are comparable both in terms of **known** and **unknown** prognostic factors
- Any “time effects” are balanced across arms
- All other advantages of prospective research

But …

- All other disadvantages of prospective research …
  - Expensive
  - Time consuming
  - Regulation
  - Logistics

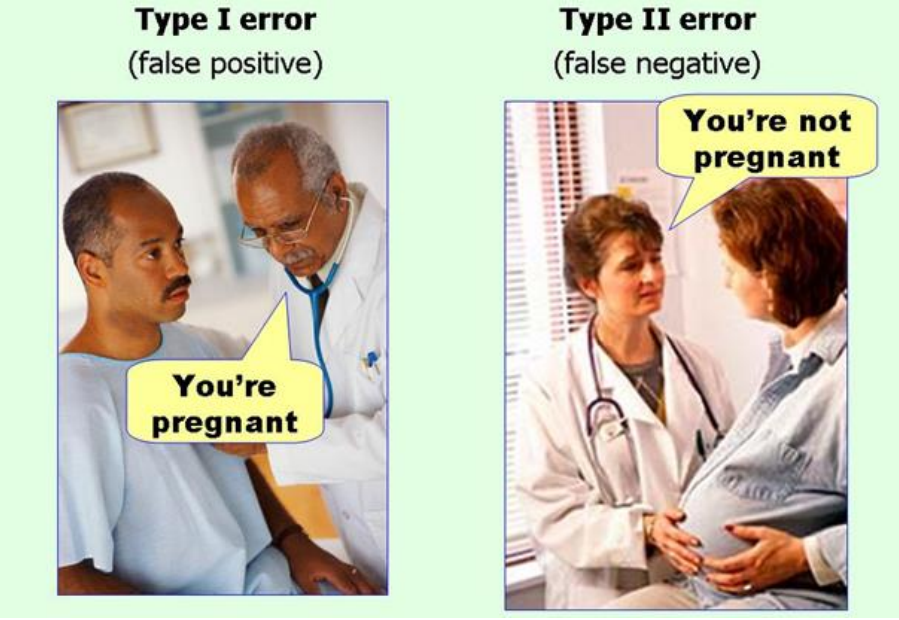
Evidence based medicine



How many patients?

Size is determined to be most efficient to detect a targeted treatment effect that is considered clinically relevant, given some pre-specified design characteristics

- As with any assay or test looking for a yes/no answer, we can make a mistake



- False positive: 5-20%
- False negative: 10-20%

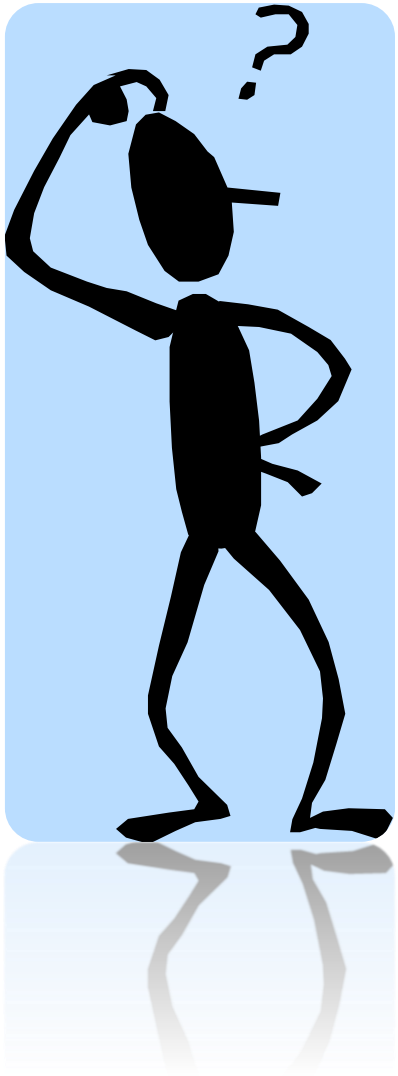
(linked to "power" of a study)

With all of this in place …

Phase III RCT **success rates** still only around **40%.**

Compared to preceding phase II studies

- Comparative rather than single arm
  - Active vs historical control
- Population more heterogeneous
  - Less selected?
- Different endpoints (surrogates?)
- Smaller observed treatment effects
  - Meaningfull effects?



What about rare cancers?

Same issues but, in addition, pressure for

- smaller but cost-effective trials
- preferably non-randomized but still rigorously controlled studies
- more flexible, adaptive designs

Several international initiatives

- Large international collaborations to stimulate and facilitate the development of clinical trials for patients with **rare cancers**
  - International Rare Cancers Initiative (IRCI; http://www.irci.info/) focuses on interventional (usually **randomized**) clinical trials
  - Rare Cancers Europe (http://www.rarecancerseurope.org/) is a multi-stakeholder initiative to put rare cancers on the European policy agenda
- **Non-cancer** specific initiatives
  - Integrated design and Analysis of small population group trial (IDeAl)
  - Innovation in small populations research (InSPiRe)
  - Advances in small trials design for regulatory innovation and excellence (ASTERIX)
- …

IRCI International Rare Cancers Initiative
Aspiring to improve the lives of patients with rare cancers

Clinical trial designs for rare diseases: studies developed and discussed by the international rare cancers initiative

Table 1
Trial names and registration.

Short name	Full name	Registration number
BALLAD/IRCI 002	A study to evaluate the potential benefit of adjuvant chemotherapy for small bowel adenocarcinoma (SBA)	Pending application
Androgen deprivation therapy in advanced SGCs/IRCI 007	A randomised phase II study to evaluate the efficacy and safety of chemotherapy (CT) versus androgen deprivation therapy (ADT) in patients with recurrent and/or metastatic, androgen receptor (AR) expressing, salivary gland cancer (SGCs)	NCT01969578
HGUS/IRCI 006	A randomised double-blind phase II study evaluating the role of maintenance therapy with cabozantinib in High Grade Undifferentiated Uterine Sarcoma (HGUS) after stabilization or response to doxorubicin +/- ifosfamide following surgery or in metastatic first line treatment	EudraCT 2013-000762-11; NCT01979393
InterAACT/IRCI 003	An International multicentre open label randomised phase II Advanced Anal Cancer Trial comparing cisplatin plus 5-fluorouracil versus carboplatin plus weekly paclitaxel in patients with inoperable locally recurrent or metastatic disease	NCT02051868
rEECur	Trial of chemotherapy for relapsed and refractory Ewing sarcoma	ISRCTN36453794
GOG-0277/IRCI 001	A phase III randomised trial of gemcitabine plus docetaxel followed by doxorubicin versus observation for uterus-limited, high-grade uterine leiomyosarcoma	EudraCT 2012-002852-17; NCT01533207
MEKi ± AKTi in UM/IRCI 005	A randomised two-arm Phase II study of Trametinib alone and in combination with GSK2141795 in patients with advanced uveal melanoma	EudraCT number – 2013-002925-50; NCT01979523
InPACT/IRCI 004	International Penile Advanced Cancer Trial	NCT02305654

- Allow more uncertainty using a randomized design with relaxed design characteristics (*IRCI 007 SGC*)
  - **Type I error rate (alpha):** probability of a false positive
  - **Power:** probability of finding a meaningful effect

Randomized study
Outcome: time to event
Targeted difference:
HR = 0.65

Alpha \ Power	90%	85%	80%	75%
5%	**227**	194	170	150
10%	185	155	134	116
15%	160	133	113	97
20%	142	116	98	**83**

Number of events obtained from EAST 6.0

Need to be careful with the consequences of relaxing the errors, given that it is unlikely that another trial will be conducted to confirm the results

IRCI 007 (EORTC) is still recruiting

Incorporate Bayesian elements

- *IRCI 002 Small Bowel Adenocarcinoma*
  - Use relaxed type I error as in previous example
    - Power: 80-90%, Type I error: 20% (one-sided), HR = 0.75
  - If significant, combine with clinician estimates of treatment benefit based on external evidence to provide a more robust estimate

Not open yet (clinicaltrials.gov)

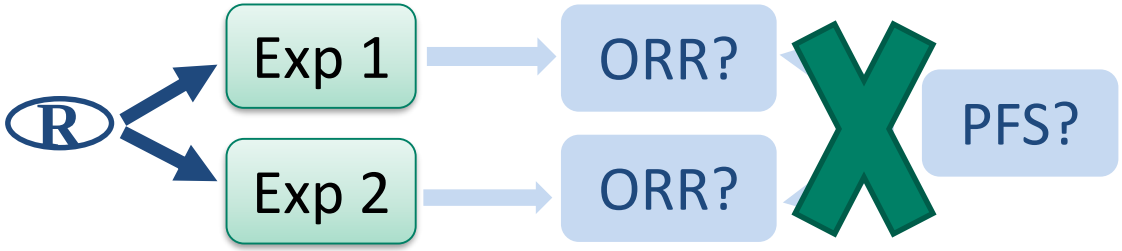
- *IRCI 004 Advanced Penile Cancer*
  - Reverse philosophy: see how many patients could be recruited and then assess whether data has sufficient value
  - Rather than focusing on hypothesis testing, this study would focus on estimation, combining with different prior assumptions (non-informative, sceptic, extreme sceptic, enthusiast)

Not open yet (clinicaltrials.gov)

- Abandon a treatment early for lack-of-benefit
  - Using aggressive interim look for futility (*IRCI 001 uLMS)*

Closed for poor accrual

  - In the absence of a control arm, using comparative final analysis and non-comparative interim analyses (*IRCI 005 Uveal melanoma*)



ASCO 2016

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Not open yet

Recruiting

Recruiting

Recruiting

Recruiting

Closed for poor accrual

Closed for futility

Not open yet

Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper

P. G. Casali[1*], P. Bruzzi[2], J. Bogaerts[3] & J.-Y. Blay[4] on behalf of the Rare Cancers Europe (RCE) Consensus Panel

Annals of Oncology 26: 300–306, 2015
doi:10.1093/annonc/mdu459
Published online 1 October 2014

- Clinical decision-making in rare cancers should allow **higher degree of uncertainty** and make use of all available knowledge and innovative approaches
- Consider **adaptive trials**, research **biomarkers** and **Bayesian** approaches to factor in all available evidence
- Use **surrogate** endpoints
- Use of **reference networks** and patient registries across Europe, involving centers of expertise to improve study recruitment and participation, patient access to information and quality of care

Next presentations

Thank you