Madrid, September 29, 2014

Trials in rare cancers
What could have been done

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2001

"*In most rare tumors, the available evidence on the effectiveness of treatments is based on few small studies of questionable methodology*"

- Retrospective Case Series
- Uncontrolled trials
- Randomized trials of small size

Activity or surrogate endpoints

- Exclusions
- Pubblication Bias

Conventional Statistical Rules

- A study **must** have an adequate size

Unjustified Implication

- If an adequate size cannot be attained, no methodological ties

Small size → **Poor quality**

Typical report

- Prospectively designed?
- (Classified as a Phase II trial)
- No Randomised controls
- Lack of planned comparisons with historical controls
- Primary endpoint: Objective response
- No statistical plan

Case Series

ESMO 2014 – Present session

STS (2009-2014)

- 6 studies
- 1 adjuvant, 5 metastatic
- All prospective trials
- 4 RTC’s
- Endpoint: TTP (1) RR (1) PFS (2) OS (2)
- Size:
  - Phase II: 24, 56, 270
  - Phase III: 228, 351, 711

ESMO 2014 – Present session

Glioblastoma – R. Stupp (2010-2014)

- 5 studies
- All prospective trials
- 4 phase III, all RTC's, 1 Phase I-II
- Endpoint: OS and/or PFS (5) Tox/RR (1)
- Size:
  - Phase I/II: 118
  - Phase III: 266, 545, 637, 921

1st Conclusion

The quality of clinical research in rare tumors has dramatically improved, and thanks to large cooperative efforts, it is now comparable to that in more frequent tumors

Critical points in STS trials (by Hans Gelderblom)

1. Lack of randomised studies
2. Lack of histotype directed studies in STS:
3. Lack of info on PFS before therapy when PFS is an endpoint
4. Lack of patients because diseases get rarer
5. Lack of info how to hit the target and lack of histotype direction

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Critical points in STS trials

1. *Lack of randomised studies*
2. Lack of histotype directed studies in STS:

Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial *Woll PJ et al* Lancet Onc 2012

Histotype directed studies in STS?

Strong evidence in support of a different efficacy of the experimental treatment in different histotypes?

YES: Trial in specific histotypes (Note: In the past, *wrong predictions)*

NO: Randomise all histotypes and plan subgroup analyses

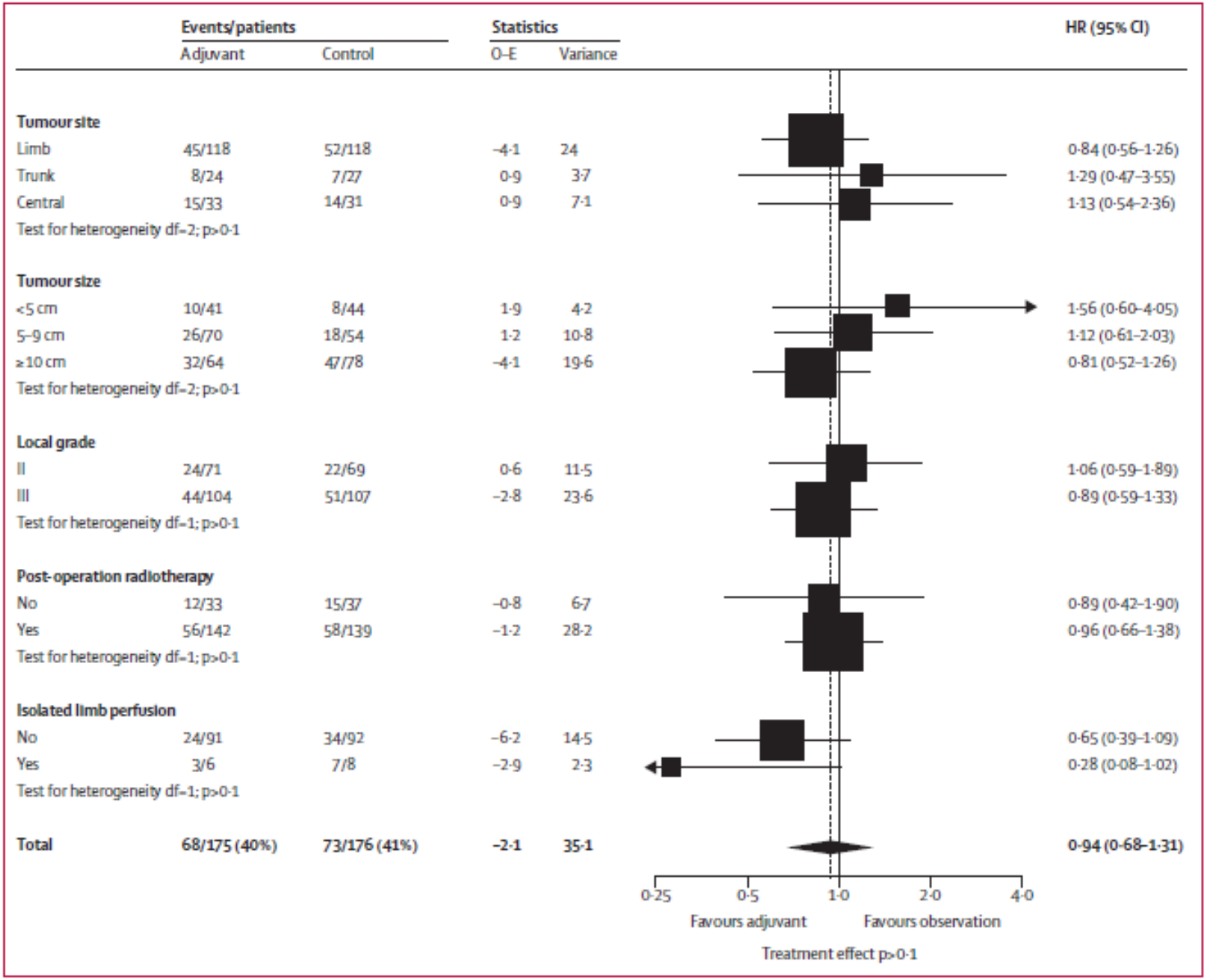


Figure 3: Effects of adjuvant chemotherapy on overall survival for patients with different baseline prognostic factors

Critical points in STS trials

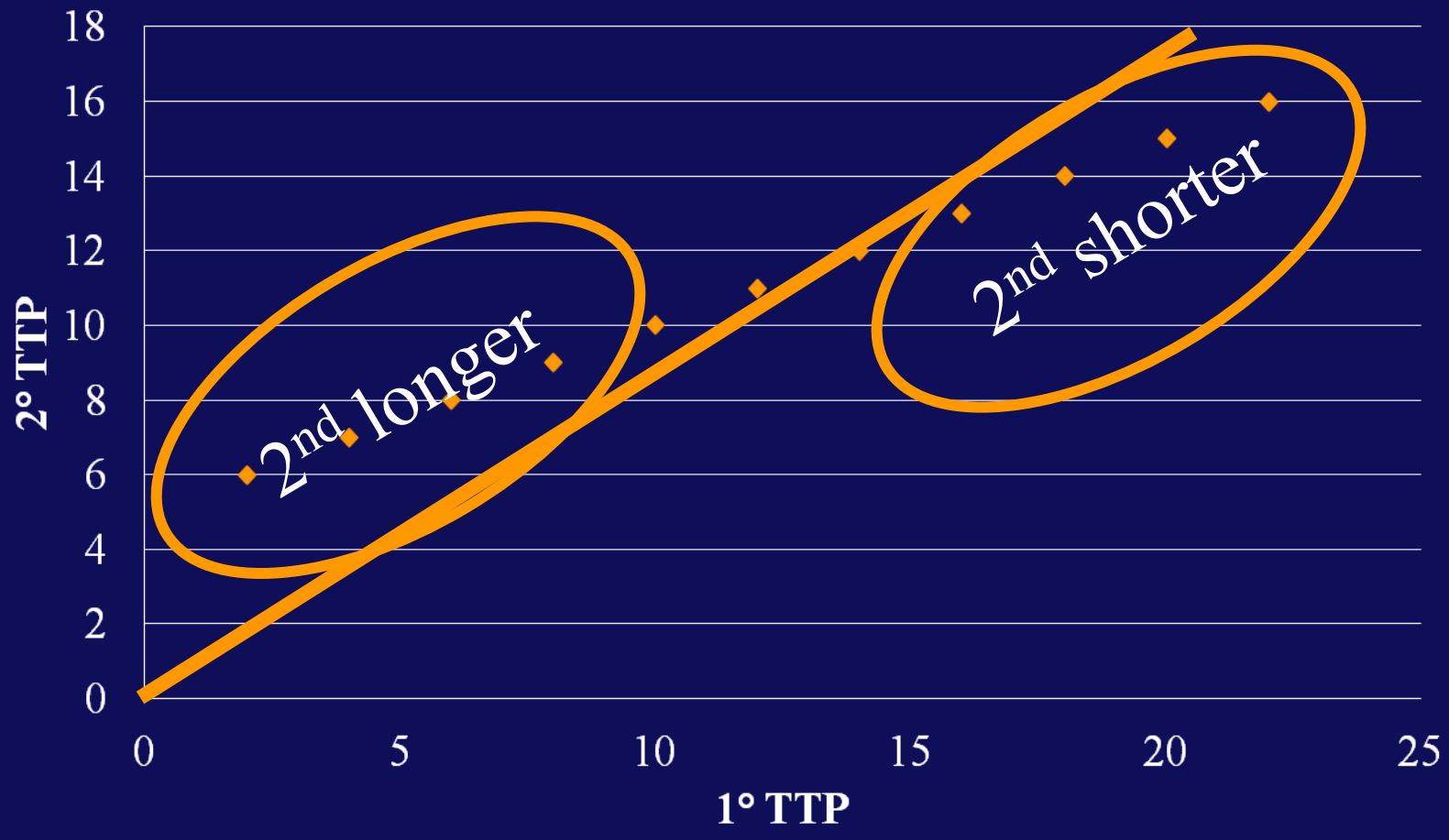
1. Lack of randomised studies

2. Lack of histotype directed studies in STS:

3. Lack of info on PFS before therapy when PFS is an endpoint

PFS before therapy may be helpful in phase II trials but it is statistically invalid (regression to the mean + selection)

Comparison of PFS before after therapy in the same patients (effect of regression to the mean)



Critical points in sarcoma trials

1. Lack of randomised studies

2. Lack of histotype directed studies in STS:

3. Lack of info on PFS before therapy when PFS is an endpoint

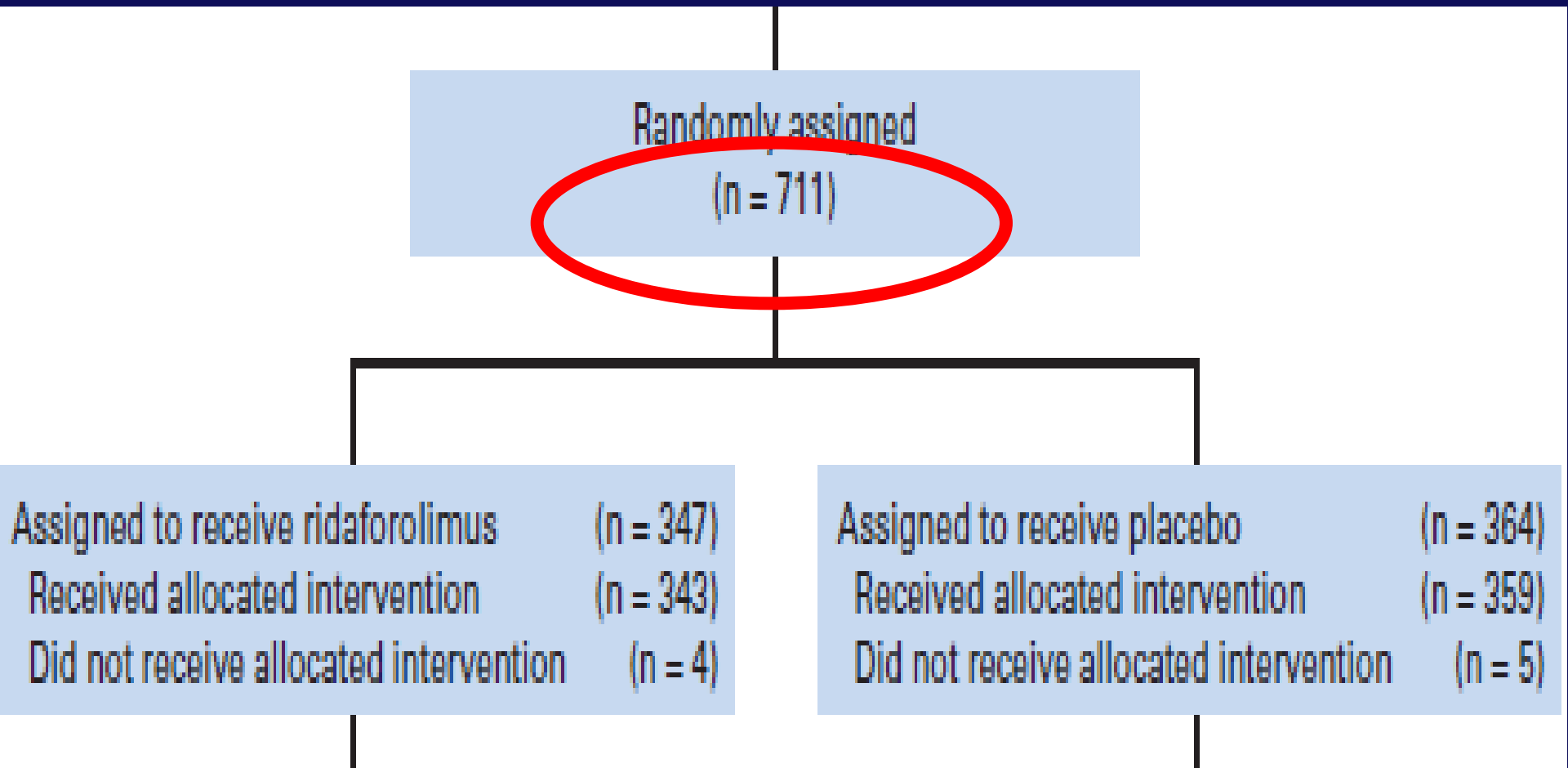
4. Lack of patients because diseases get rarer

5. Lack of info how to hit the target and lack of histotype direction

Demetri et al. …RCT of m-TOR ib in metastatic Sarcomas …(JCO 2013)

- Pts age>13yrs with metastatic sarcomas of either soft tissue or bone origin.
- Certain histopathologic subtypes (alveolar soft part sarcoma, GIST) were excluded. Pts with bone sarcomas were required to have measurable soft tissue (lung or liver) metastases.
- Current SD CR PR after >3 cycles and <12 cycles of 1^{st}, 2^{nd}, 3^{rd} line CTX chemotherapy

Demetri et al. …RCT of m-TOR ib in metastatic Sarcomas …(JCO 2013)



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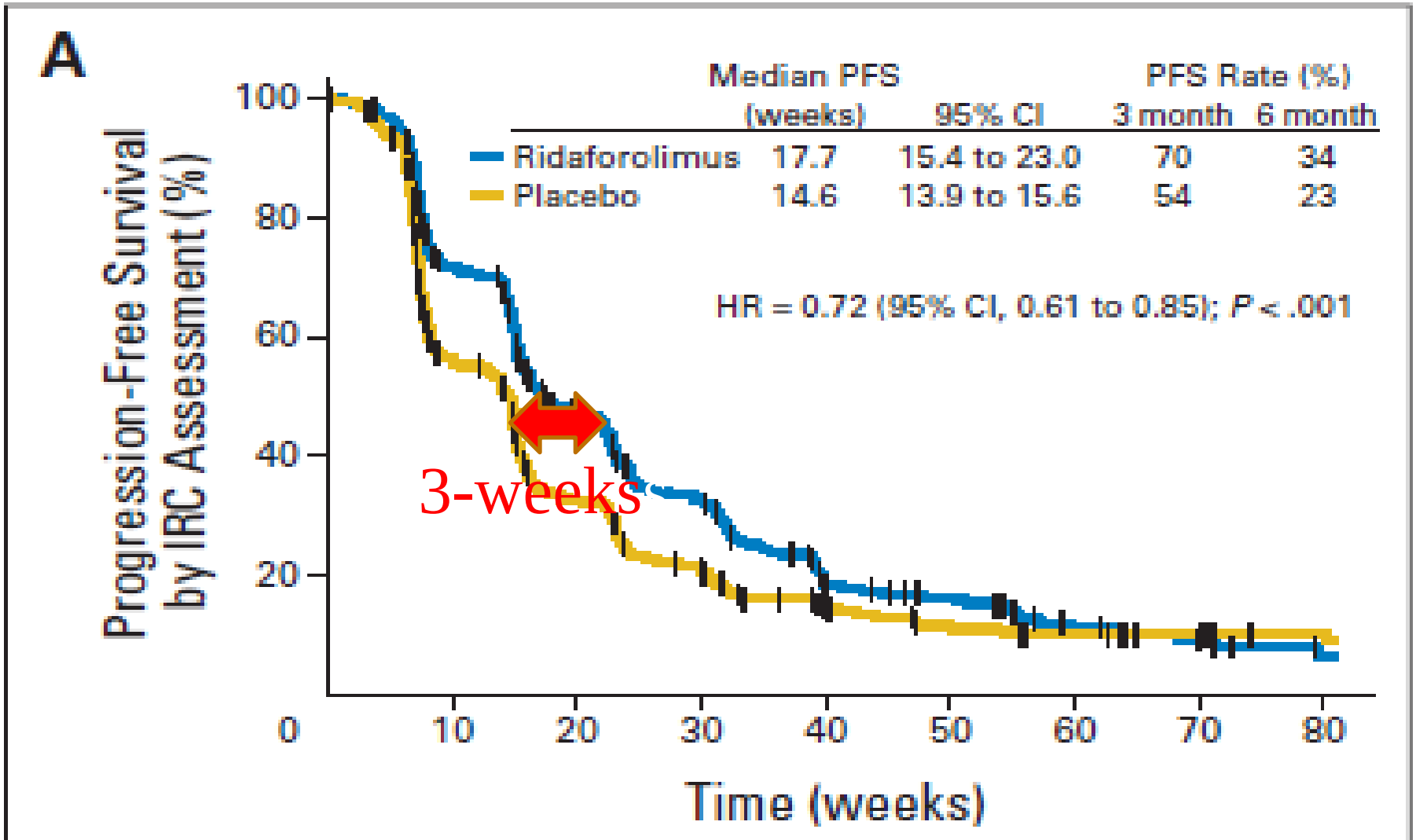
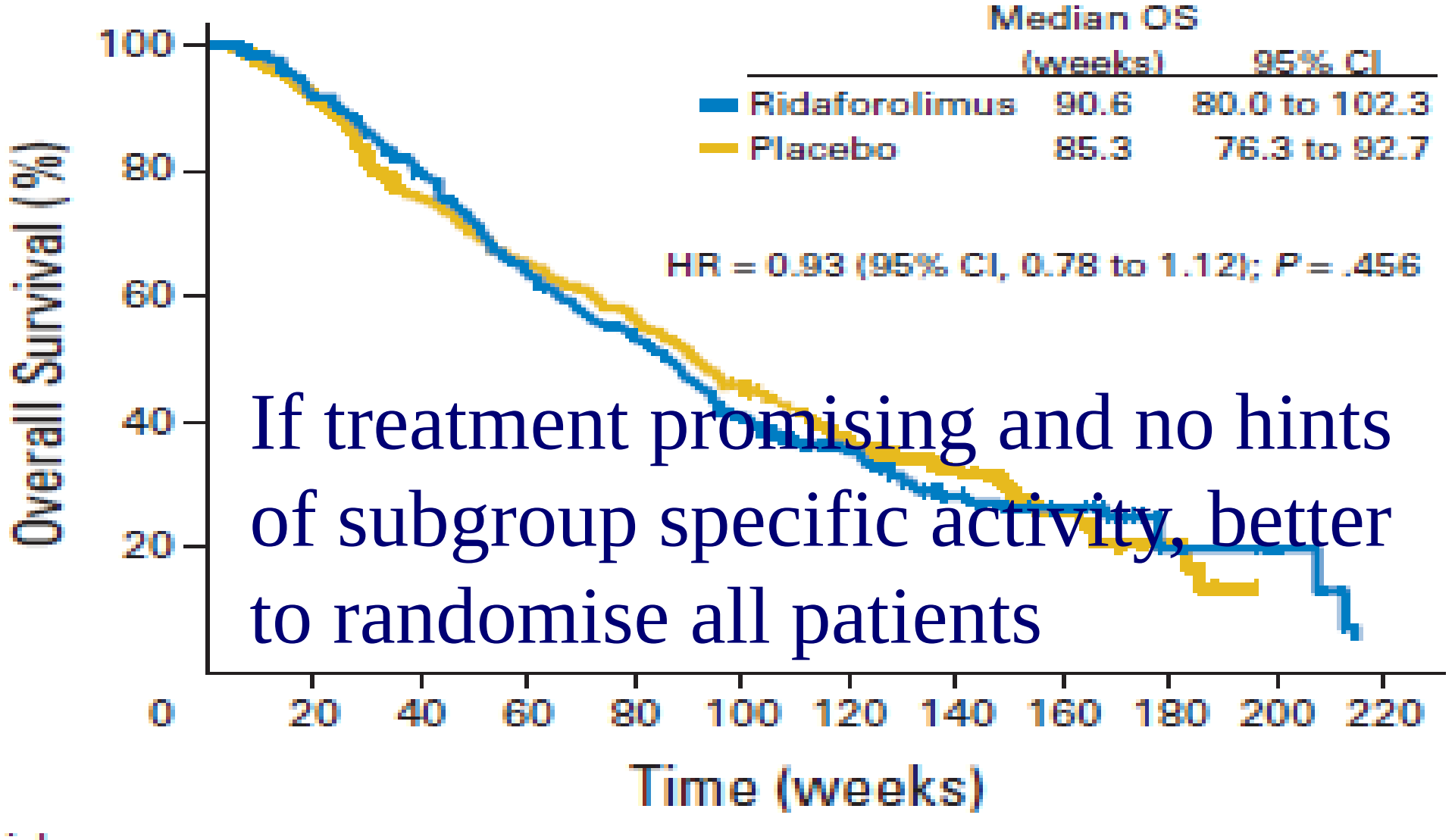


Demetri et al. …RCT of m-TOR ib in metastatic Sarcomas …(JCO 2013)

- 3- weeks improvement in PFS
- 11% (4%) more patients progression-free at 6 months (1 year)
- No evidence of heterogeneity in subgroups
- Molecular subgroups?
- Better to wait for phase II evidence of activity in subgroups?

Demetri et al. …RCT of m-TOR ib in metastatic Sarcomas …(JCO 2013)



If treatment promising and no hints of subgroup specific activity, better to randomise all patients

Critical points in STS trials (by Hans Gelderblom)

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Critical points in STS trials

1. Lack of randomised studies

Should we do randomised studies or use controls from registries?

Critical points in sarcoma trials

1. Lack of randomised studies

2. Lack of histotype directed studies in STS:

3. Lack of info on PFS before therapy when PFS is an endpoint

4. Lack of patients because diseases get rarer

In very rare molecular subgroups, should we still try to have a randomised control group?

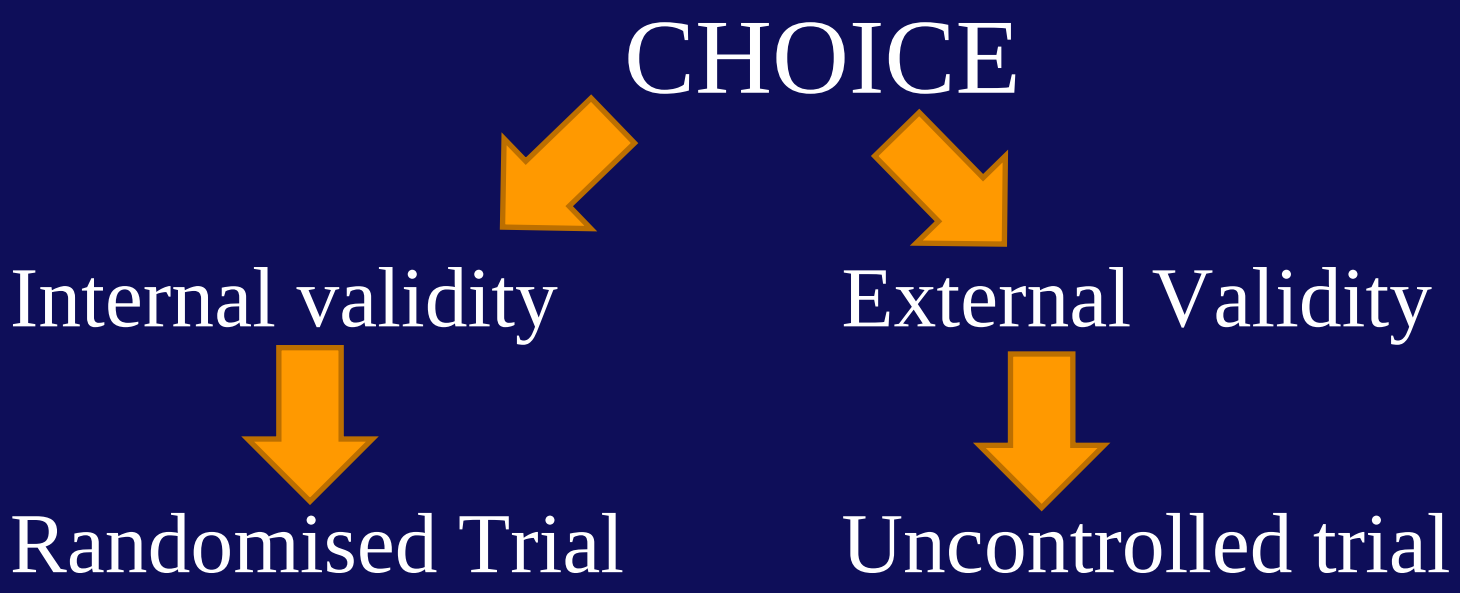
CLARIFICATION!

- Phase II → Uncontrolled
- Phase III → Rand. Contr. Trials

PHASE ⟺ AIMS!

- Phase II → Activity
- Phase III → Efficacy

Efficacy trial in a Rare Condition



Design ⟷ Interpretation

1. Internal Validity

   Is it true?

2. External Validity

   So what?

1. Internal Validity
   - Statistical Validity, absence of bias/systematic error
   - Results = Truth +/- Chance

- *Internal Validity:*
  - *Statistical Validity, absence of bias/systematic error*
  - *Results = Truth +/- Chance*

- **<u>External Validity</u>**:

Possibility to
- Extrapolate
- Generalise
- Apply

the results of the study

Checklist - Internal Validity

- *Rationale*
- *Primary Aim*
- *Design*
- **Unbiased assessment of the Endpoint**
- **Registr./Randomization**
- *Selection Criteria*
- *Treatment Protocol*
- Statistical Plan
- *Interpretation of Results*

External Validity

- **INTERNAL VALIDITY**
- Study Design (Contrast)
- Selection Criteria/Patients Characteristics
- Participating Centers
- Treatment Protocol –Follow-up Protocol
- Endpoint
- Compliance – Contamination
- Precision of the estimates
- Analysis ‘intention to treat’

Efficacy trial in a Rare Condition

CHOICE

Internal validity

Randomised Trial

Pro: Unbiased estimates of treatment effects

Con's: More difficult to enroll patients

Less Patients on new treatment

(Ethical Problems?)

Efficacy trial in a Rare Condition

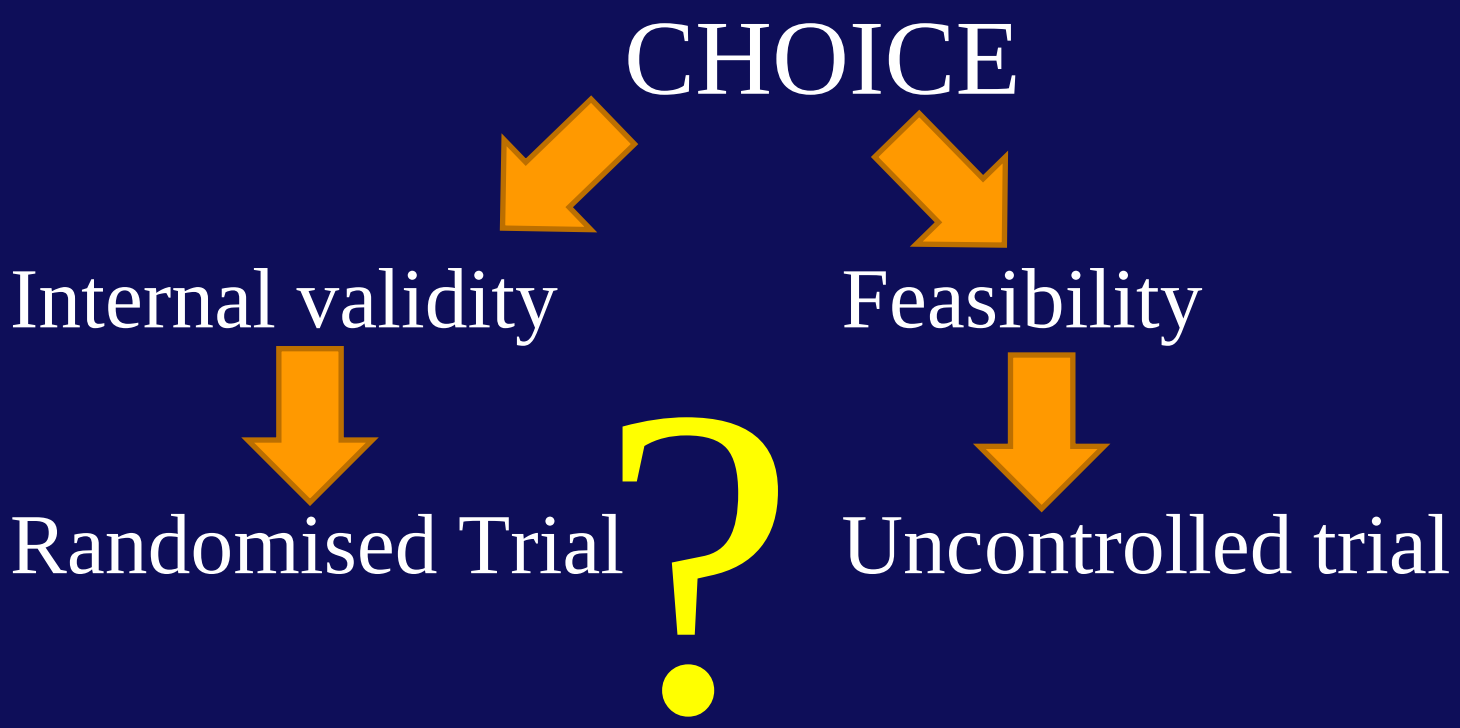
CHOICE

Feasibility

Uncontrolled trial

Pro's: More patients on new treatment (Activity, Toxicity) - Easier to recruit patients
Larger historical (control) group
Con's: **BIAS!!!**

Efficacy trial in a Rare Condition



Examples

Efficacy and Safety of **Trabectedin** in Patients With Advanced or Metastatic **Liposarcoma or Leiomyosarcoma** After Failure of Prior Anthracyclines and Ifosfamide: Results of a Randomized Phase II Study of Two different Schedules

Demetri GD et al, JCO 2009

Demetri et al JCO 2009 - RATIONALE

The efficacy of trabectedin 1.5 mg/sqm (q3 weeks 24-hour) in pts with heavily pretreated, STS was previously evaluated **in three nonrandomized** phase II studies. A pooled analysis suggested slightly more efficacy in liposarcomas and leiomyosarcomas.

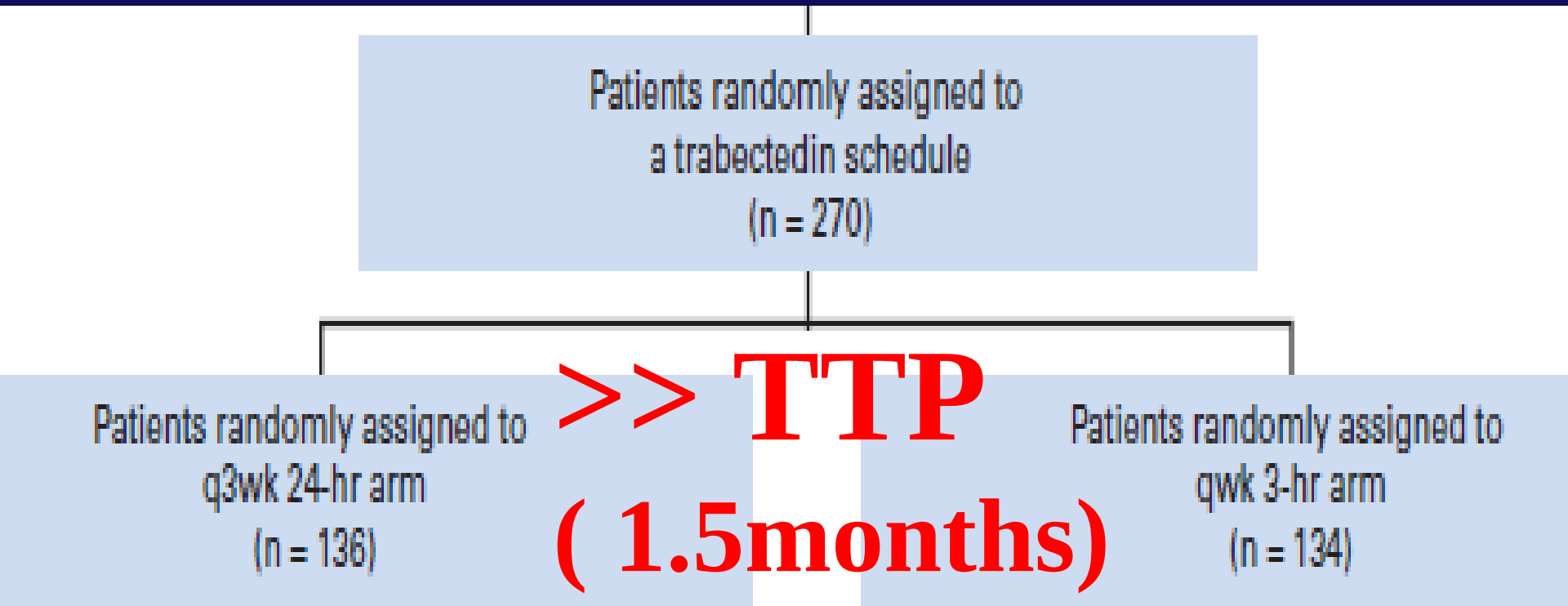
PHASE II

AIMS

A weekly trabectedin schedule (0.58 mg/m2 3-hour IV infusion for 3 consecutive weeks in a 4-week cycle had substantial anticancer activity in pretreated ovarian carcinoma

Demetri et al JCO 2009

Advanced lipo/leiomyosarcoma – Previous Anthra & IFO - <3 previous CTX, and >4 wks since last CTX
Relatively good conditions



>> TTP (1.5months)

Demetri et al JCO 2009

- Phase II Aims?

Perfectly met:

Median TTP 3.7 vs 2.3 mos (HR, 0.73; *P= 0 .03)*

Median PFS 3.3 vs 2.3 mos (HR, 0.75; P .04)

q3 weeks 24-hour arm better than qwk 3-hour

- Phase III Aims?

Demetri et al JCO 2009

-Efficacy of Trabectedin in pretreated Advanced lipo/leiomyosarcoma? Historical controls?

-No mention in the results!

Discussion: *"The median OS of 13.9 mos (q3 weeks) and 11.8 mos (qwk) are very favorable in the context of an expected 6-month survival range for a patient population of advanced/metastatic STS having progressed after anthracyclines and ifosfamide."*

Demetri et al JCO 2009

- Lost opportunity ? (The study had >90% power toward a 60% increase in TTP (2-sided 5% p) after 217 TTP events. – An increase of 1.5 months in TTP was statistically significant)

- An untreated control group realistic? (Advanced lipo/leiomyosarcoma – Previous Anthra & IFO - <3 previous CTX, and >4 wks since last CTX)

- Vs another off-label regimen? -> phase II

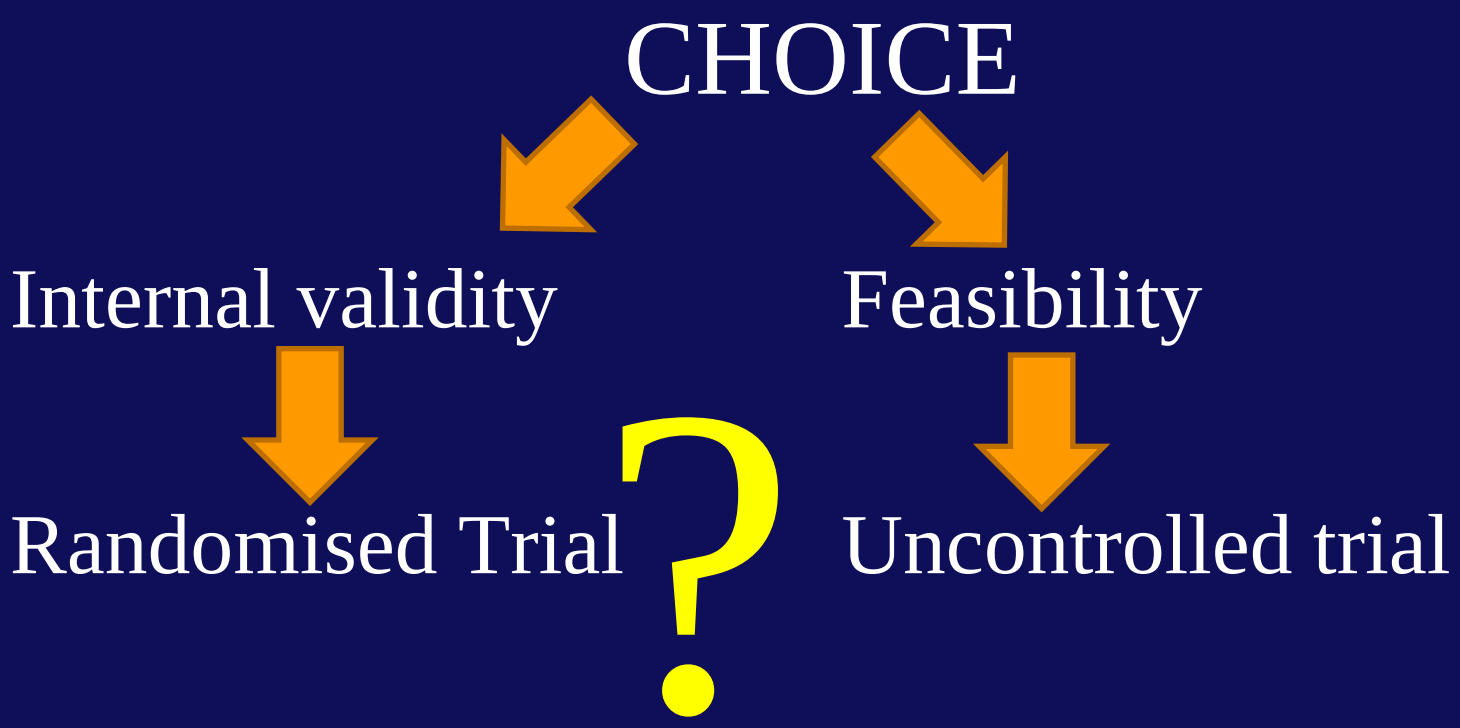
Stacchiotti JCO 2012

Phase II of Imatinib in Chordoma

Uncontrolled, 56 patients,

Conclusions: "...confirms that imatinib has some antitumor activity in chordoma. ... The lack of RECIST responses and the potentially slow natural course of the disease ... ***do not allow us to affirm that this treatment is effective****"*

Efficacy trial in a Rare Condition



Last 2 decades

- New drugs -> New methods (Phase I-II)

- New Patients-> New methods (Phase II-III)
  - Prognostic subgroups
  - Patients with the target
  - ‘Evaluable’ patients

{ **RARE!**

Modern Phase II-III Trials

?

New Methodologies?

Recent statistical developments (<10 yrs) in rare cancers

- Surrogate endpoints

Less patients in less time

Stronger effects

Recent statistical developments (<10 yrs) in rare cancers

- Surrogate endpoints
- Adaptive trials

More efficient trials – Less patients/less time – Stronger effects

Recent statistical developments (<10 yrs) in rare cancers

- Surrogate endpoints
- Adaptive trials
- New types of systematic reviews

Collect and assemble all the pertinent evidence

Recent statistical developments (<10 yrs) in rare cancers

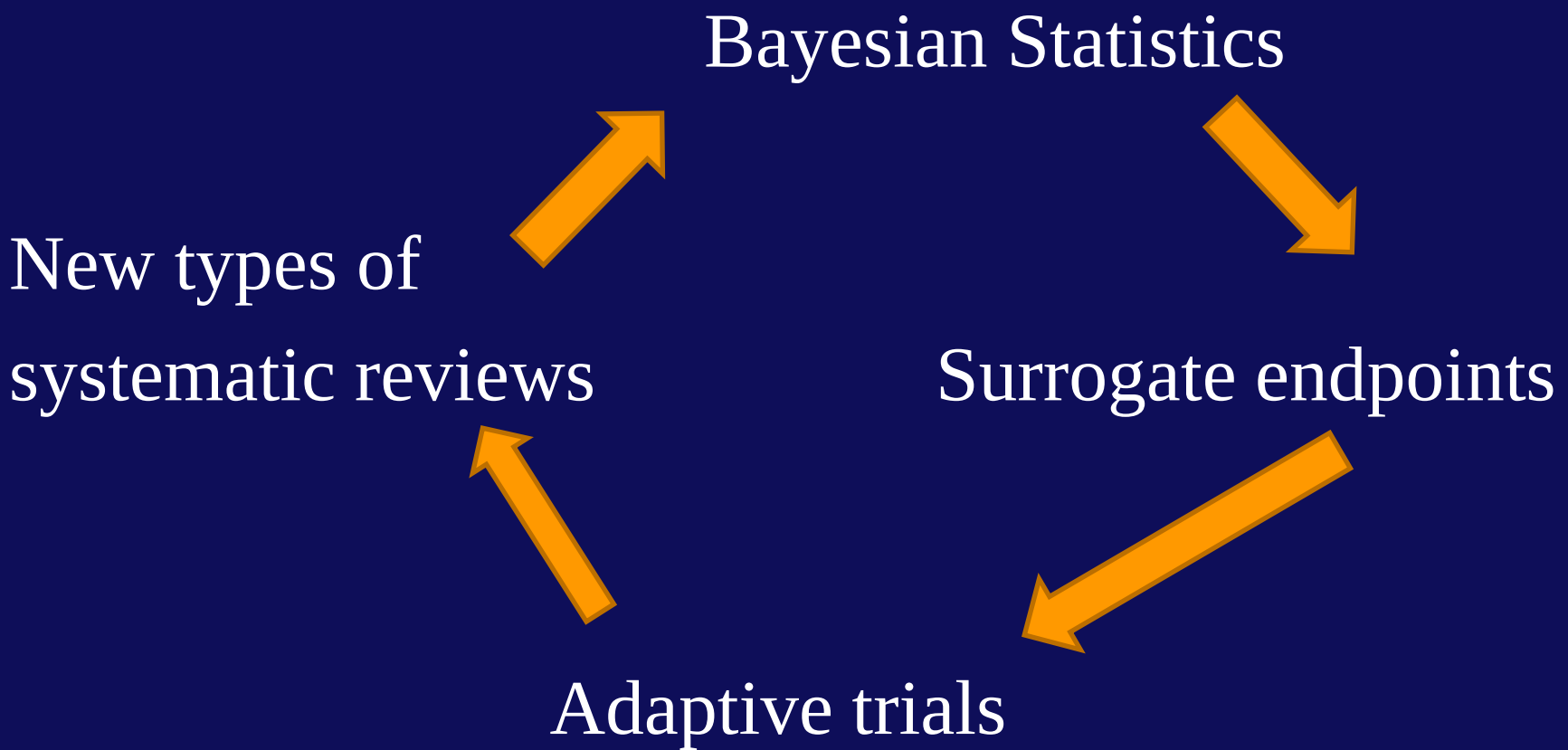
- Surrogate endpoints
- Adaptive trials
- New types of systematic reviews
- **Bayesian Statistics**

Recent statistical developments (<10 yrs) in rare cancers

- Surrogate endpoints
- Adaptive trials
- New types of systematic reviews
- Bayesian Statistics

AIM AT LARGER EFFECTS!

Recent developments (<10 yrs) in rare cancers



New generation of efficacy trials (aimed at larger effects)

- Uncontrolled efficacy (phase II-III) trials of high quality with historical controls
- Randomized activity (Phase II) trials followed by uncontrolled efficacy studies (with historical controls)
- RCT's with **surrogate** endpoints
- Adaptive, Bayesian, activity/efficacy RCT's
- Multi-site, mutation-driven trials

Randomised Clinical Trial

- Identification of study aim(s)
- Explicit selection criteria
- Random treatment assignment
- Reliable/unbiased assessment of the endpoint
- Statistical Plan

Clinical Trial with no randomized control group

- Identification of study aim(s)
- Explicit selection criteria
- Arbitray treatment assignment: BIAS??
- Reliable/unbiased assessment of the endpoint
- Statistical Plan

Clinical Trial with no randomized control group

- Identification of study aim(s)
- Explicit selection criteria
- CONSECUTIVE ELIGIBLE PATIENTS WITH PLANNED COMPARISONS WITH HISTORICAL CONTROL GROUPS

Prospective Population-based Registries to provide Historical Controls for trials?

LARGE EFFECTS LOOKED FOR

Chordomas

- Prior Evidence in support of Imatinb: Quite Strong
- Factors against RCT: Rarity, Slow Growth, No control treatment
- Better to have 28 pts on Gleevec and 28 untreated controls or 56 pts with chordoma on Gleevec and 200 historical controls?

Other challenges cited by Roger Stupp for Glioblastoma

- Rapid Progression
- Blood B
- ...kers
- ...action with other drugs
- Difficult to assess response
- Informed consent

Clinical problems with major implications for the design of the study

Conclusion (2)

- The conventional rigid distinction between early and late phases of the development of new drugs is going to be lost, especially in rare tumors (seamless phase II-III trials)

- The methodology of clinical trials will undergo radical changes reflecting the improvements in clinical knowledge/method