



ACT EU Multi-Stakeholder Workshop
on Methodology Guidance: A patient-
centred approach to methodologies

23 November 2023
Hybrid meeting

Beyond RCTs

Ethical view on a use case

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Use case provided by
Pr David Pérol

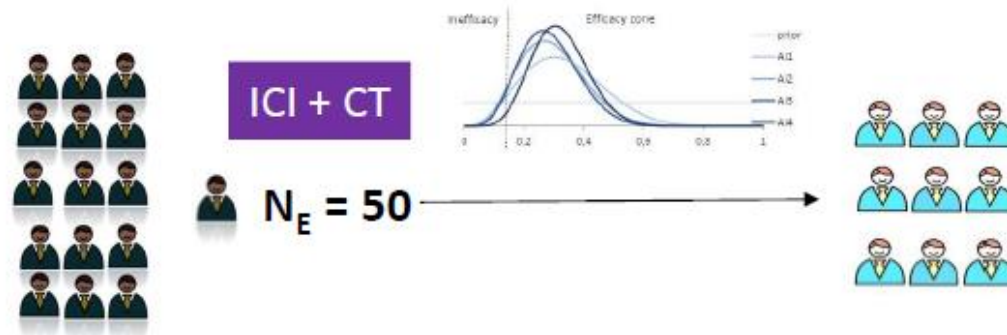


Case Study: Large-Cell Neuroendocrine Lung Carcinoma (LCNEC)

- Uncontrolled, single-arm phase II trial
- External comparison (survival) from the largest European Real-World database (ESME lung database)
- Target trial emulation² combined to advanced statistical adjustment techniques to control for confounding biases³

1. Single-arm part

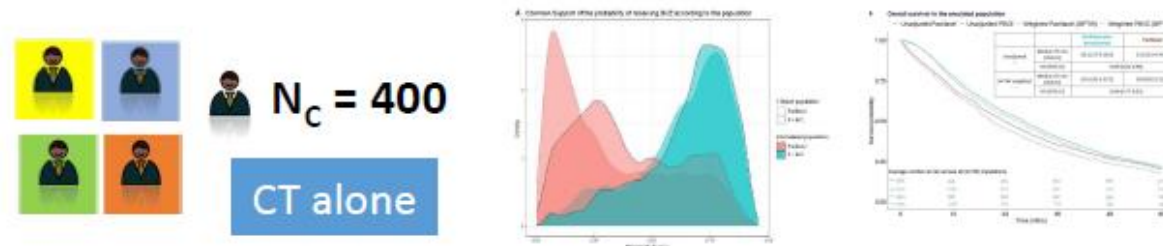
Bayesian Design



2. External comparison

Real World-Data

ESME-AMLC database¹



1. Griesinger F. Lung Cancer 2022. 2. Hernán M. N Engl J Med. 2021 3. Antoine A. J Natl Cancer Inst 2023.

Ethical view: Key points (1/2)

1. General considerations

- Technical: Not RCT clinical trial (gold-standard) => Useful or futile clinical trial?

Position of the trial in the drug development plan ? Subsequent trial(s) ?

Acceptability for 1) CT authorization, 2) MA (EMA) and 3) reimbursement procedure (HTA)

- . Procedural: **1 CT + 1 study on Data?** ; 'Combine clinical trial'?

=> Ethics Committee scope of competence ?

2. Single-arm part : Issues, questions / relevance of the design

- **Small sample size** => Rare lung tumors (≈2% of lung neoplasms), recruiting potential = 50 pt in 3 Y
=> Poor prognosis: median OS = 8 months for advanced LCNEC
- **No comparator arm** => Randomization non-feasible from a practical viewpoint (time, sponsoring...)
. Rare tumors, CRT: 164 pts with 80% power)

Ethical view: Key points (2/2)

3. External comparison

- **A priori definition** of the clinical question, study population, intervention, comparator and outcomes in a protocol and statistical analysis plan?
- **Sources for external control:** relevant?
- **Methods aiming to avoid bias?**
 - including:
 - . target trial emulation to mitigate selection and temporality biases,
 - . g-computation to address confounding bias,
 - . and use of negative and positive controls to explore residual confounding

To 'conclude'...

- **RCT remains the gold-standard**
- **Possible ways of harmonizing to provide convincing evidence?**



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