Could we do without RCTs? The use of single-arm studies as a basis for approval: a meta epidemiologic pilot study.

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Introduction

- Number of marketing authorization (MA) based on single arm studies (SaS) is increasing, mainly in oncology.
 - SaS raise many questions: such designs are prone to biases specific to descriptive studies: confounding factors and methods used for external comparisons that do not allow the same level of evidence as a RCT.
- Risks of External control design** : Atezolizumab (IMvigor211)¹ & Nivolumab (Checkmate-331)² received FDA accelerated approval on the basis of SaS results, pending a confirmatory study
→ phases III studies were **inconclusive** concerning primary efficacy outcome
- Use of SaS and external control designs must be limited and restricted as specified by the **ICH E10**³ guidelines: « *situations in which the effect of treatment is dramatic and the usual course of the disease highly predictable* ».

Objective

A pilot study to describe the main characteristics and methodology of SaS conducted in oncology «to get a MA » or « as proof of efficacy »

Results

Publication selection: A total of **2451 articles** have been found with the combination of MeSH terms on Medline

- The step of sorting relevant articles is in progress. This pilot study on 12 articles has been done to illustrate the interest of our study.
- Preliminary results of the pilot study are presented below:

Table 1: Main characteristics of SaS

Characteristics	%	Number
Phase	Phase II	100% 12
Type of sponsor	Industrial	100% 12
Primary outcome	Overall Response Rate (ORR)	100% 12
Molecule type	Small molecule	50% 6
	Monoclonal Antibodies	50% 6
Cancer Type	Hematology	58% 7
	Solid cancer	42% 5
Type of external comparison	Historical control	33% 4
	Prefix norme	33% 4
	No formal comparison	25% 3
	Before after	8% 1
	ITT	58% 7
Population of analysis	mITT	33% 4
	FAS	8% 1
Registration	FDA and EMA	25% 3
	FDA only	67% 8
	Ongoing	8 % 1
Number of studies for registration	1	36% 4
	2	55% 6
	3	9% 1
	Yes	36% 4
Confirmatory study	No	55% 6
	Ongoing	9% 1
	Yes	75% 3
Consistency of results Phase II → Phase III	No	25% 1
Number of Centers	Mean ±Standard Deviation; Mediane	61 ± 42 ; 48
	Range	272 ± 281 ; 185
Number of Subjects included		21-1069

Figure 1: Mode Of Action

Figure 2: Type of Cancer

Figure 3: Type of External Comparison

Conclusion

- Feasibility of this study has been confirmed with this pilot study.
- 2/3 of SAS are compared with others studies which represented external comparisons → This has led to stronger decisions to prove the benefit of treatment.
- 1/3 are compared with informal comparisons that may require more attention to their acceptance.
- SaS publications are not well indexed in the Medline database, which required significant manual removal work for irrelevant articles.

Publications selection

- Inclusion criteria:** phase II or III pivotal SaS, antineoplastic agents, publication date 2003 - 2019
- Non-inclusion criteria:** observational studies, SaS without aims of external comparison (pure single arm), RCTs.

Study design

Meta-epidemiological study

Outcome

To describe methodology concerning external comparison

Statistical analysis

To identify the key features of the methodology of the SaS and comparators used to prove efficacy, using descriptive statistics.

Data extraction

- Coarsely removal by hand of irrelevant articles
- Application of the inclusion criteria for the ambiguous articles
- Systematic extraction of data from selected articles

Data sources

Medline database using a combination of MeSH terms

Single arm, Antineoplastic agents, Phase II, Phase III, not RCT, effective, safe, proof of efficacy

A 10% objective response, based on objective response achieved with second-line chemotherapy, was used as a historical control to determine the sample size for the cohort with tumour PD-L1 expression of 5% or greater. Assuming a target objective response of 30%, 70 treated patients with PD-L1 expression of 5% or greater would provide a 99-1% power at 5% type I error to reject the null hypothesis of a two-sided test that the true objective response was 10%. Assuming a 32% prevalence of PD-L1

scenarios were examined. Under the assumption that 80 patients would have measurable disease per independent central review, two-sided 95% exact CIs for the proportion of patients who achieved an objective response would be 16-0-35-9 or 29-2-51-6, provided the observed proportion of patients who achieved an objective response was 25-0% (based on 20/80 patients responding) or 40-0% (based on 32/80 patients responding). For each of these scenarios, the sample size was considered to provide sufficient precision for the treatment effect estimation, given the width of the CIs.

assessed over the full follow-up of the study. Activity analysis done for 70 patients after 36 week assessment provides 90% or higher power (at two-sided α of 5%) to reject the null hypothesis of 40% of patients achieving an overall response.^{1,2,3-7} An overall response rate in favour of an alternative hypothesis was 60% (based on data available at the time of study design, which preceded publication of kinase inhibitor studies). Safety and all other activity

Discussion

In many studies, the type of external comparison is not specified, which increased the risk of making decisions without prior comparison.

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