Société Française de Pharmacologie et de Thérapeutique

La rentrée de la Méthodologie

Les analyses en sous-groupes

Enfin une solution avec la hiérarchisation

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SAINBIOSE

INSERM UMR 1059

Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: Contribution of the DHEAge Study to a sociobiomedical issue

Table 2. Bone turnover: BMD parameters (mg/cm²) between M0 and M12

	Men <70		Men >70		Women <70		Women >70	
Bone	Placebo	DHEA	Placebo	DHEA	Placebo	DHEA	Placebo	DHEA
Neck	+7 (−8, +37)	+7 (−9, +31)	+1 (−10, +15)	+4 (−14, +32)	−9 (−16, +18)	+13 (+1, +30)*	+6 (−7, +36)	+5 (−8, +32)
Trochanter	+1 (−12, +16)	+5 (−6, +12)	+6 (−12, 15)	0 (−13, +2)	−3 (−14, +17)	+2 (−13, 12)	−4 (−14, +6)	+4 (−11, +15)
Intertrochanter	+9 (−22, +32)	−2 (−28, +21)	−2 (−27, +28)	+6 (−12, +22)	−5 (−23, +23)	+1 (−8, +23)	−2 (−31, +13)	+15 (−18, +30)
Total hip	+13 (−8, +27)	+8 (−21, +22)	+7 (−8, +21)	+10 (−10, +23)	+9 (−13, +24)	+6 (−4, +28)	+4 (−13, +21)	+13 (−1, +27)
Ward's	+20 (−31, +59)	+8 (−21, +22)	+5 (−14, +33)	+10 (−24, +19)	−23 (−40, +6)	+4 (−19, +25)*	−5 (−25, +24)	−1 (−30, +10)
Upper radius	0 (−12, +10)	−9 (−19, +8)	+4 (−8, +21)	−3 (−19, +10)	−6 (−18, +8)	0 (−15, +12)	−10 (−19, +5)	+4 (−8, +14)*
Mid radius	+1 (−12, +10)	−5 (−16, +10)	−4 (−18, +7)	−1 (−9, +6)	−4 (−20, +9)	−8 (−22, +0)	−9 (−23, +6)	+1 (−8, +14)
Proximal radius	−3 (−18, +7)	−2 (−14, +10)	−1 (−12, +7)	−1 (−10, +1)	−1 (−12, +4)	−3 (−14, +4)	−5 (−12, +6)	+2 (−7, +13)
Total radius	0 (−12, +8)	−4 (−20, +6)	−1 (−12, +7)	−1 (−10, +1)	−6 (−17, +4)	−7 (−22, +6)	−11 (−20, +5)	+2 (−5, +10)*

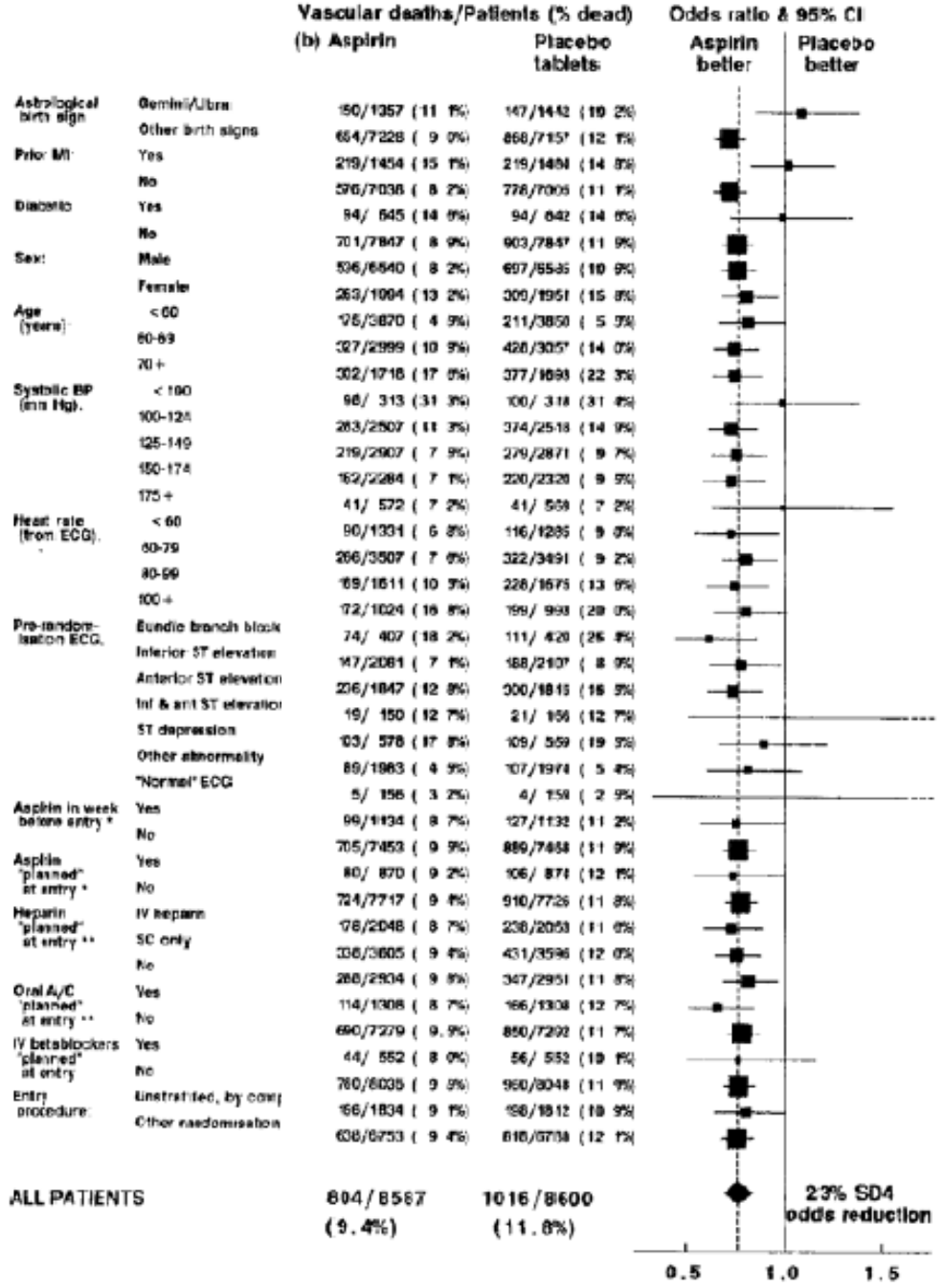
Data are given as median (1st, 3rd quartiles). *, $P < 0.05$ vs. placebo group of same age and same gender.

Baulieu EE et al. PNAS 2000

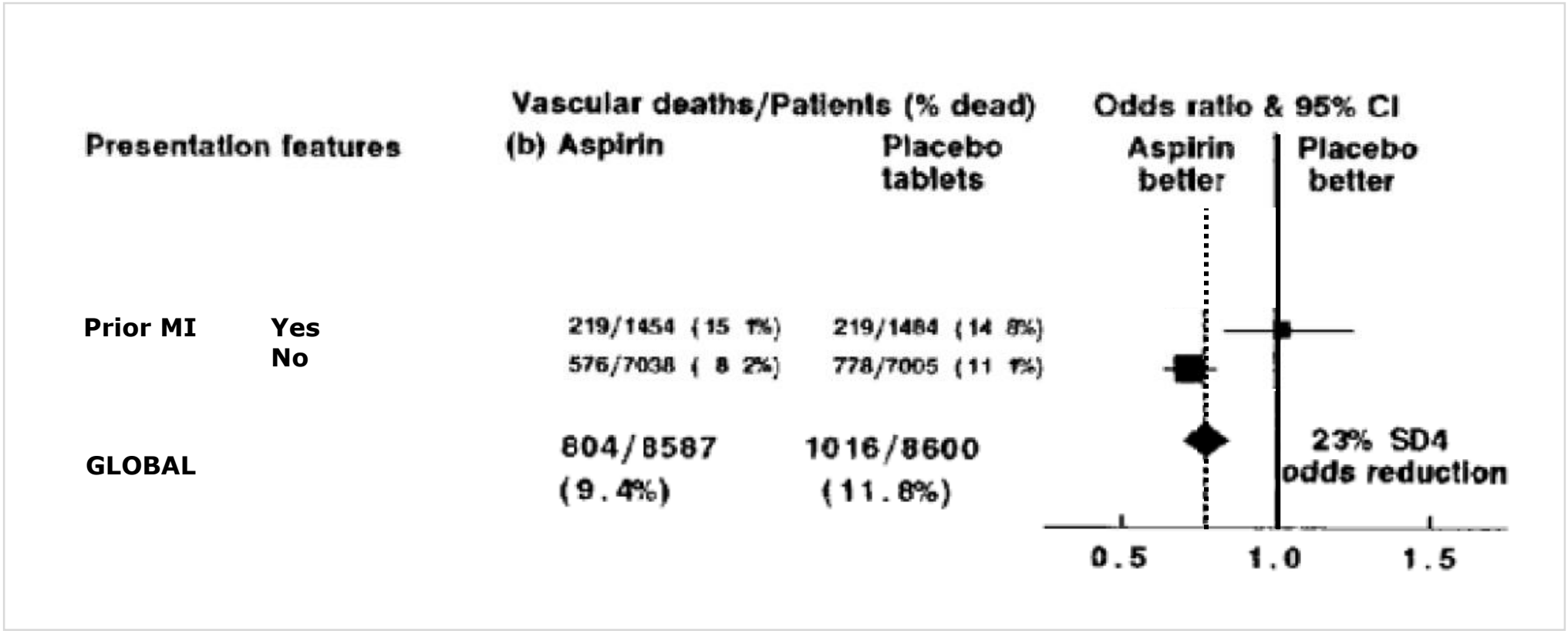
RANDOMISED TRIAL OF INTRAVENOUS STRPTOKINASE, ORAL ASPIRINE, BOTH, OR NEITHER AMONG 17 187 CASES OF SUSPECTED EACUTE MYOCARDIAL INFARCTION: ISIS-2

Aspirine vs Placebo

RRR= **23**% [**15**%;**30**%]
P < 0.0001



ISIS-2. Lancet 1988



ISIS – Lancet 1988

Situations de multiplicité des tests

Multiplicité des critères de jugement

Analyses intermédiaires pour efficacité

Plus de 2 groupes de traitement

Analyses en sous-groupes

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 19 September 2002
CPMP/EWP/908/99

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POINTS TO CONSIDER ON MULTIPLICITY ISSUES IN CLINICAL TRIALS

DISCUSSION IN THE EFFICACY WORKING PARTY	January 2000
TRANSMISSION TO CPMP	July 2001
RELEASE FOR CONSULTATION	July 2001
DEADLINE FOR COMMENTS	October 2001
DISCUSSION IN THE EFFICACY WORKING PARTY	June 2002
TRANSMISSION TO CPMP	September 2002
ADOPTION BY CPMP	September 2002

http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC5

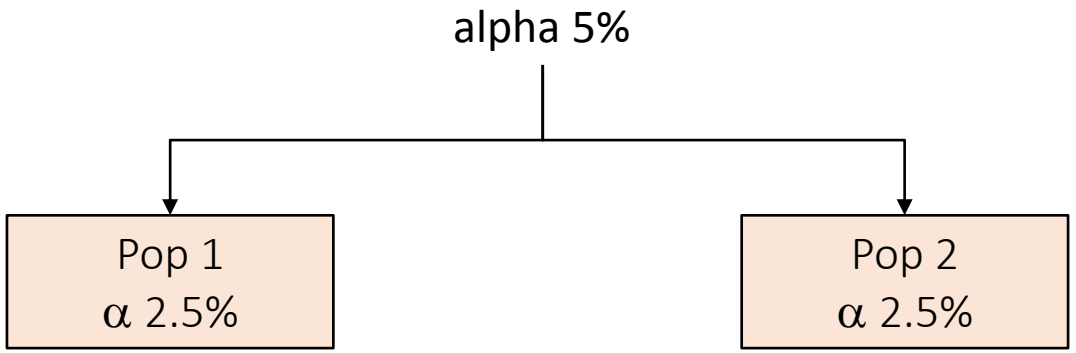
Comment prendre en compte la multiplicité des tests avec la multiplicité des critères de jugement ?

1. **Répartition du risque alpha sur plusieurs sous groupes**
2. **Répartition et ré-allocation**
3. **Hiérarchisation des analyses en sous-groupes**

1. Répartition du risque alpha sur plusieurs sous-groupes

Risque d'erreur global de 5%

- population 1 : seuil α 0.025 α 0.04
- population 2 : seuil α 0.025 α 0.005

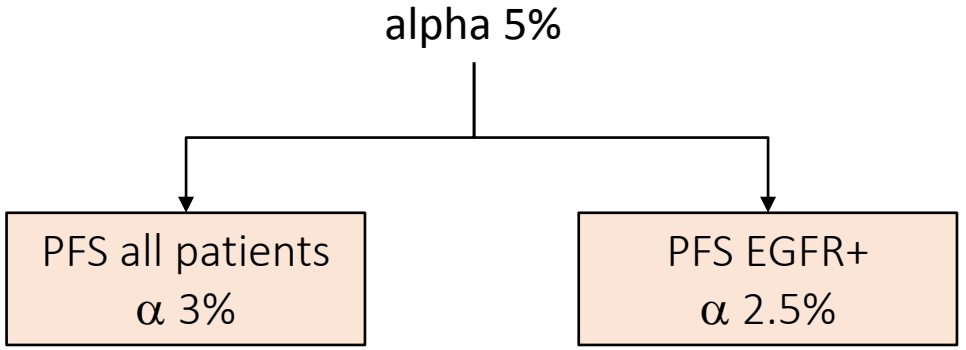


Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study

Statistical analysis

The co-primary endpoints were PFS in all analysable patients irrespective of EGFR status, and PFS in patients with EGFR immunohistochemistry-positive tumours.

The alpha level of 5% was split between the two co-primary endpoints: 3% for all patients and 2% for patients with EGFR immunohistochemistry-positive tumours.



Cappuzzo D et al. SATURN. Lancet Oncol 2010

Neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with oestrogen receptor-positive, HER2-negative, early-stage breast cancer (LORELEI): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial

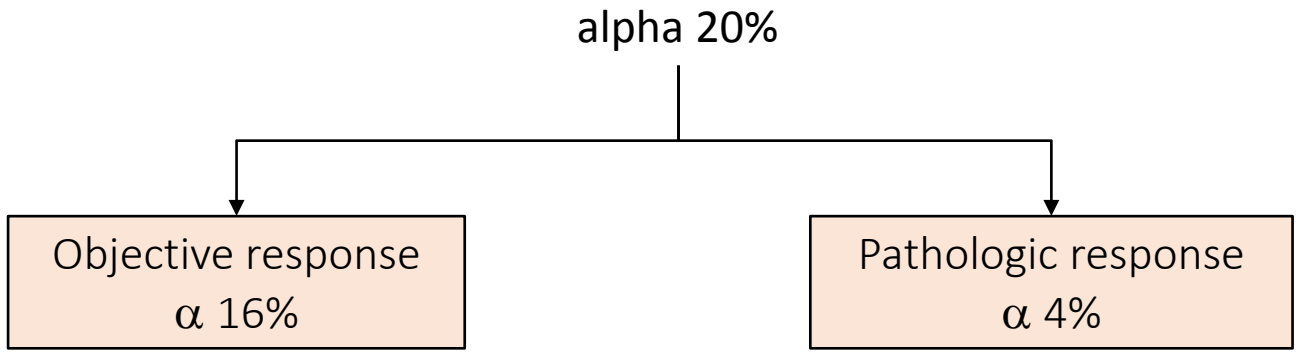
Outcomes

The coprimary endpoints for this study were the following: the proportion of patients who achieved an objective response (defined as the percentage of patients with complete or partial responses, and measured by centrally assessed MRI via modified RECIST version 1.1 criteria) in all enrolled patients and in patients with *PIK3CA*-mutant tumours; and the proportion of patients with pathological complete responses in breast and axilla (defined as ypT0/Tis, ypN0) by local evaluation in all enrolled patients and in patients with *PIK3CA*-mutant tumours.

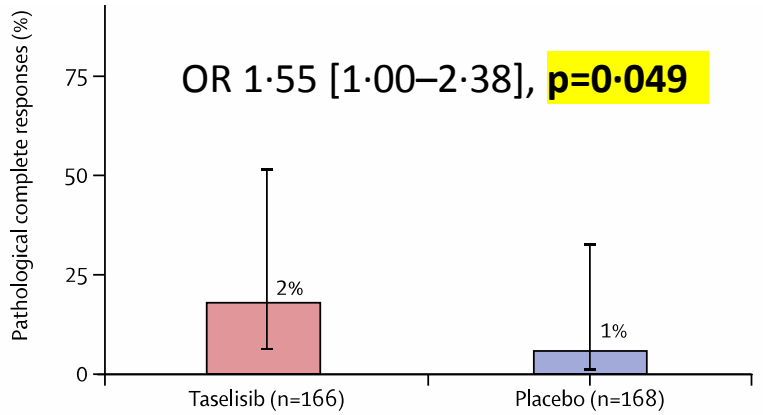
Statistical analysis

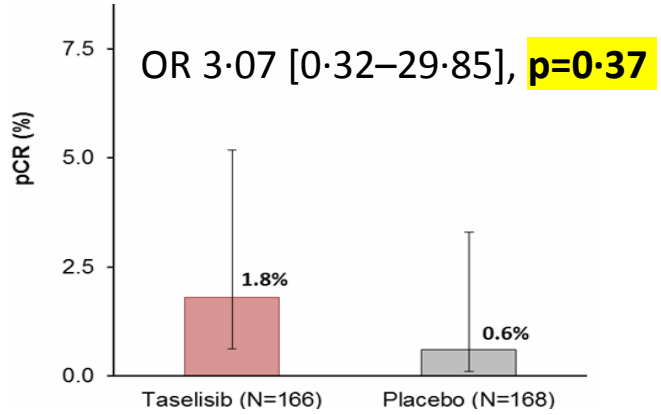
LORELEI was considered positive if either one of the coprimary endpoints was significant in all enrolled patients and in patients with *PIK3CA*-mutant tumours. Since this was an exploratory phase 2 study focused on the estimation of treatment effects, multiplicity adjustment aimed not to be too restrictive. Therefore, an overall, two-sided, family-wise type I error of 20% was used and was divided within each population into 16% for the proportion of patients who achieved an objective response and 4% for total pathological complete responses.

LORELEI. Lancet Oncol 2019

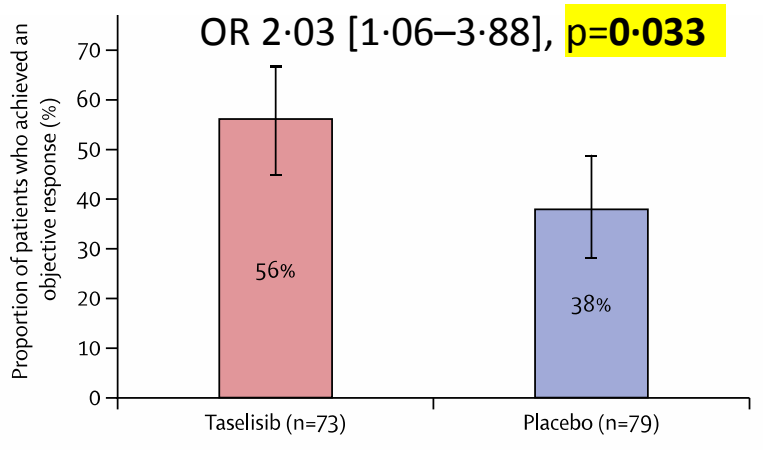


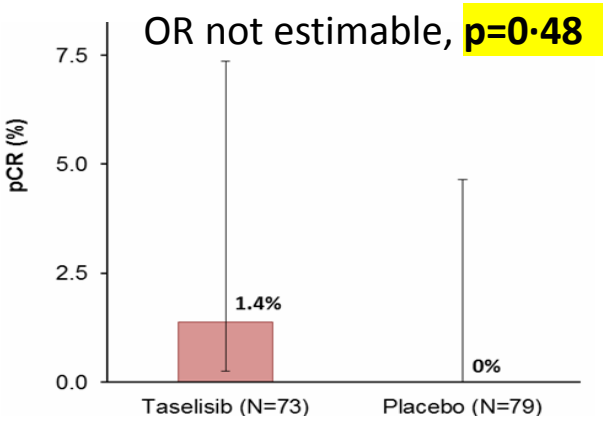
All randomized patients





PIK3CA mutants





LORELEI. Lancet Oncol 2019

1. Répartition du risque alpha sur plusieurs sous-groupes

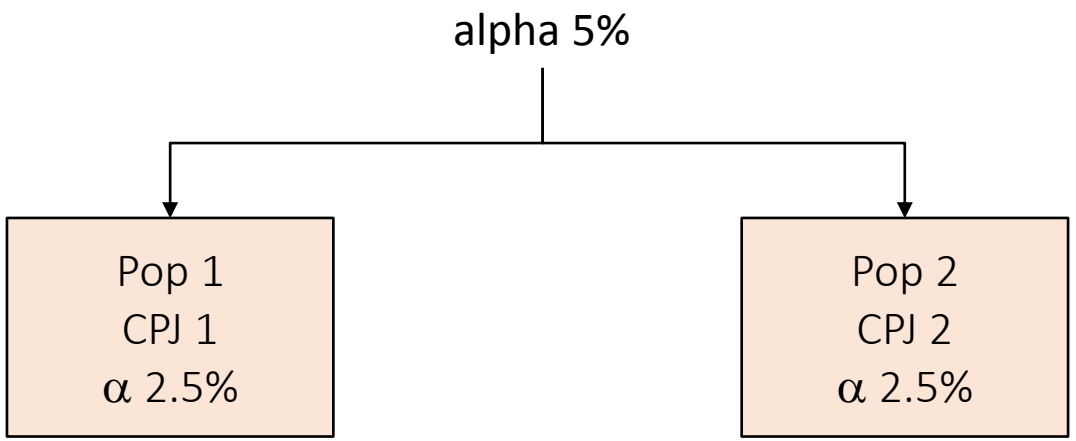
Apprendre à repenser les sous-groupes

- ‘’**Que veut-on démontrer**’’ et non ‘’Que va-t-on pouvoir trouver ???’’
- Pas suffisant de définir les sous-groupes a priori
- Souvent une seule modalité du sous-groupe
- Inflation du risque β :
  - calcul de NSN approprié
  - parcimonie

En pratique, si répartition :

- Les sous-groupes peuvent « **rattraper** » un résultat principal non significatif

Répartition du risque alpha sur plusieurs sous-groupes et critères de jugement

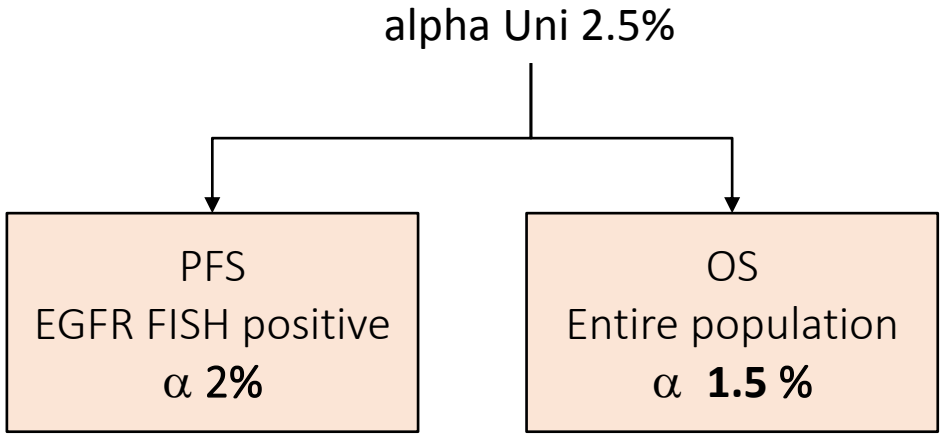


Répartition du risque alpha sur plusieurs sous-groupes et critères de jugement

Cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC (SWOG S0819): a randomised, phase 3 study

Outcomes

The co-primary endpoints were progression-free survival (defined as the duration from randomisation to progression, symptomatic deterioration, or death from any cause, whichever comes first, by RECIST 1.1 as assessed by the treating investigator) in patients who are *EGFR* FISH-positive and overall survival (defined as the duration from randomisation to death from any cause) in the entire study population. Central review of progression-



Statistical analysis

The basis for the statistical design of the study has been previously described.[16] Although the study had co-primary endpoints, the sample size was based on the primary endpoint within the *EGFR* FISH-positive population.

SWOG S0819. Clin Cancer Res 2012
SWOG S0819. Lancet Oncol 2018

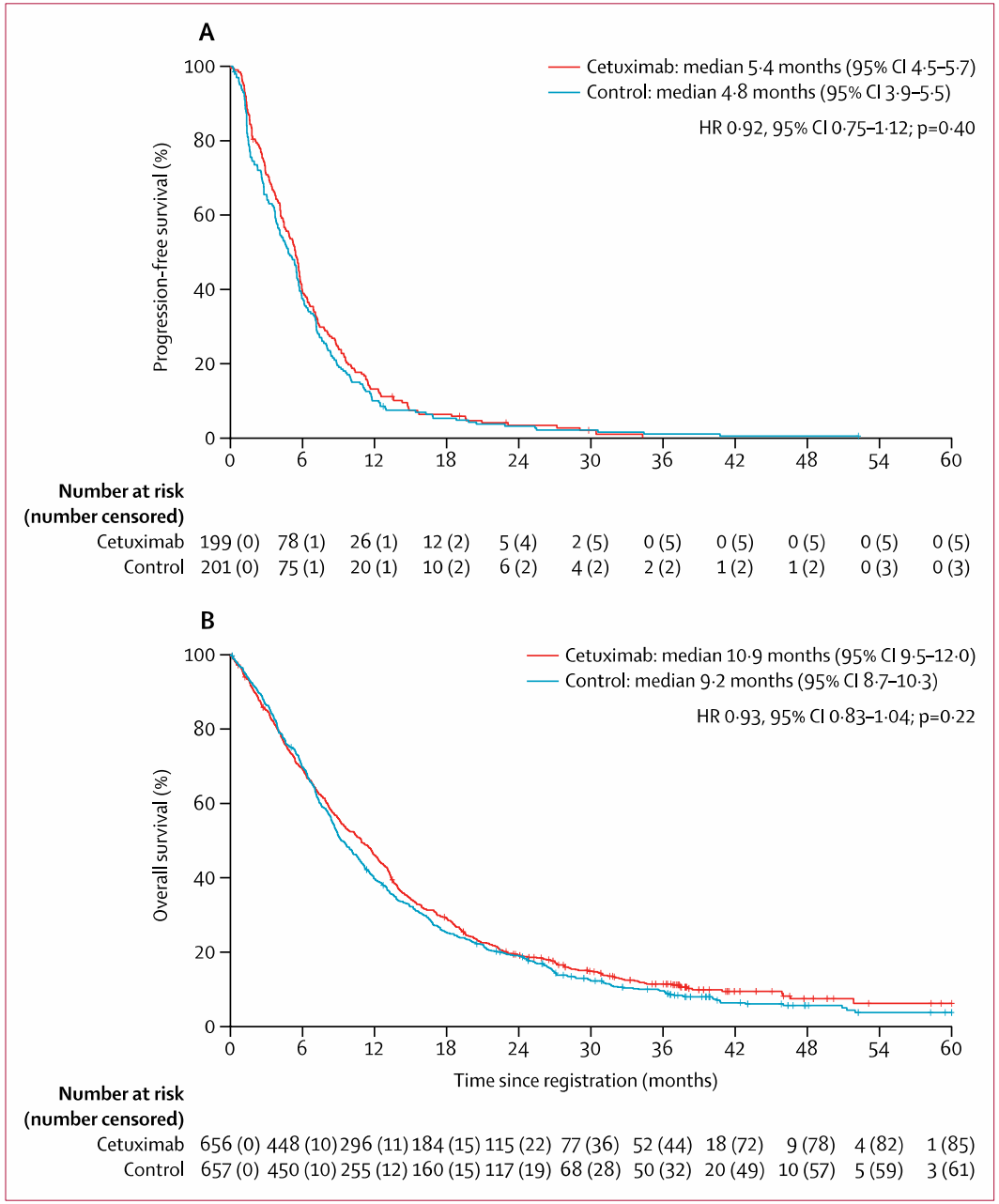
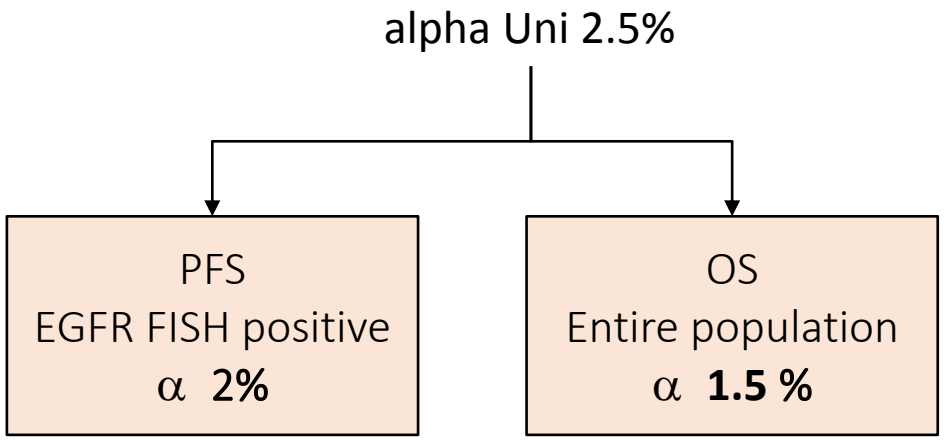


Figure 2: **Progression-free survival in patients with *EGFR* fluorescence in-situ hybridisation-positive cancers (A) and overall survival in the entire study population (B)**



2. Répartition et ré-allocation

Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial

Outcomes

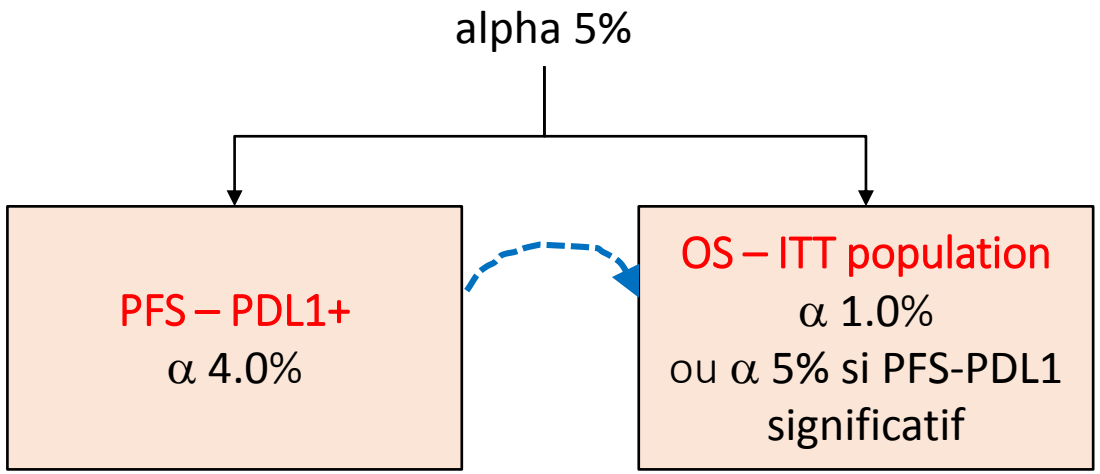
Co-primary endpoints were progression-free survival (RECIST 1.1) by investigator assessment in patients with PD-L1 positive disease (defined as ≥1% expression on tumour-infiltrating immune cells) and overall survival in the intention-to-treat (ITT) population. Key secondary objectives included overall survival in the PD-L1 positive population, progression-free survival in the ITT population, the proportion of patients who achieved an objective response, duration of response, patient-reported outcomes, and safety. Radiographic endpoints were also assessed by an IRC. A complete list of outcomes is reported in the protocol (see appendix).

IMmotion151. Lancet 2019

2. Répartition et ré-allocation

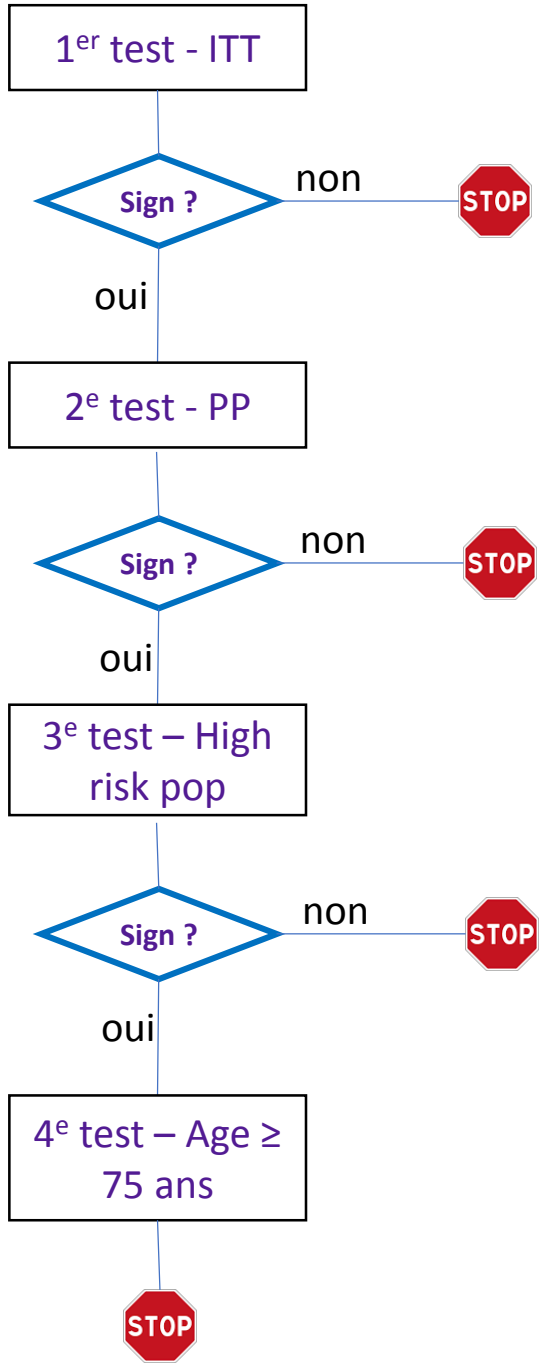
Statistical analysis

We randomly assigned 915 patients, including 362 patients with a PD-L1 immunohistochemistry tumour-infiltrating immune cell score of 1% or higher. The type 1 error (α) for the entire study is 0·05 (two-sided), which we split between the co-primary endpoints of progression-free survival in patients with PD-L1 positive disease (α=0·04) and overall survival in the ITT population (α=0·01) to ensure sufficient power to test both co-primary endpoints. If progression-free survival was significant, we recycled the α=0·04 to the overall survival in the ITT poulation.[23,24] We defined the



IMmotion151. Lancet 2019

3. Hiérarchisation des analyses en sous-groupes



3. Hiérarchisation des analyses en sous-groupes

Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients

Primary efficacy outcome
Asymptomatic prox DVT symptomatic DVT or PE, death from VTE day 47

We performed sequential analyses in 3 prespecified, progressively inclusive cohorts: patients with an elevated d-dimer level (cohort 1), patients with an elevated d-dimer level or an age of at least 75 years (cohort 2), and all the enrolled patients (overall population cohort).

The three cohorts that were included in the efficacy analysis were prespecified in a procedure with a fixed hierarchical sequence to adjust for the type I error rate. If betrixaban was superior to enoxaparin with respect to the primary efficacy outcome in cohort 1 (at an alpha level of 0.05), the trial was considered to have met its primary end point, and superiority with respect to the primary efficacy outcome was tested in cohort 2. If betrixaban was superior to enoxaparin in cohort 2, superiority with respect to the primary efficacy outcome was then evaluated in the over- all study population.

APEX. NEJM 2016

3. Hiérarchisation des analyses en sous-groupes

Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients

STATISTICAL ANALYSIS

The three cohorts that were included in the efficacy analysis were prespecified in a procedure with a fixed hierarchical sequence to adjust for the type I error rate.[19]

Table 2. Components of the Primary ar elevated d-dimer comes.* elevated d-dimer or age > 75 yrs

Outcome	Cohort 1				Cohort 2				Overall Population			
	Betrixaban (N = 1914)	Enoxaparin (N = 1956)	Relative Risk (95% CI)	P Value†	Betrixaban (N = 2842)	Enoxaparin (N = 2893)	Relative Risk (95% CI)	P Value†	Betrixaban (N = 3112)	Enoxaparin (N = 3174)	Relative Risk (95% CI)	P Value†
	no./total no. (%)				*no./total no. (%)*				*no./total no. (%)*			
Primary end point												
Primary efficacy outcome‡	132/1914 (6.9)	166/1956 (8.5)	0.81 (0.65–1.00)	0.054	160/2842 (5.6)	204/2893 (7.1)	0.80 (0.66–0.98)	0.03	165/3112 (5.3)	223/3174 (7.0)	0.76 (0.63–0.92)	0.006

APEX. NEJM 2016

Les analyses hiérarchiques

Point clé : prédéfinir la « bonne » hiérarchie

- En fonction de la pertinence clinique des critères
- En fonction de la probabilité de significativité
  - Fréquence
  - Effet
- Calcul NSN approprié…