Cancers Urologiques & Interprétation Essais Prospectifs

Focus Cancer de Prostate

THIERY-VUILLEMIN Antoine (MCUPH Oncologie Médicale CHRU Besançon)
a.thieryvuillemin@mac.com

Sommaire

- Introduction
- Exemples
- Fiche de Lecture

Niveau de Preuve et Grade de Recommandation

- **Evidence levels are mandatory.** Recommendations should be accompanied by proper evidence level and grade of recommendation according to the adapted Infectious Diseases Society of America-United States Public Health Service Grading Syst
  - Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144.
- **The Level of Evidence (LOE)** describes the quality of existing evidence (trials, cohort studies, case-control studies, expert opinion) that address a specific clinical question. The quality of evidence is assessed in terms of number of trials, sample size, methodology, bias, heterogeneity.
- **The Grade of Recommendation (GOR)** is a composite parameter, as it incorporates both the quality of evidence (as in LOE) as well as the clinical significance/magnitude of benefit or harm given by a novel therapy.

ESMO Guidelines Committee, October 2015,
latest revision October 2017

Niveau de Preuve et Grade de Recommandation

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions

Niveau de Preuve

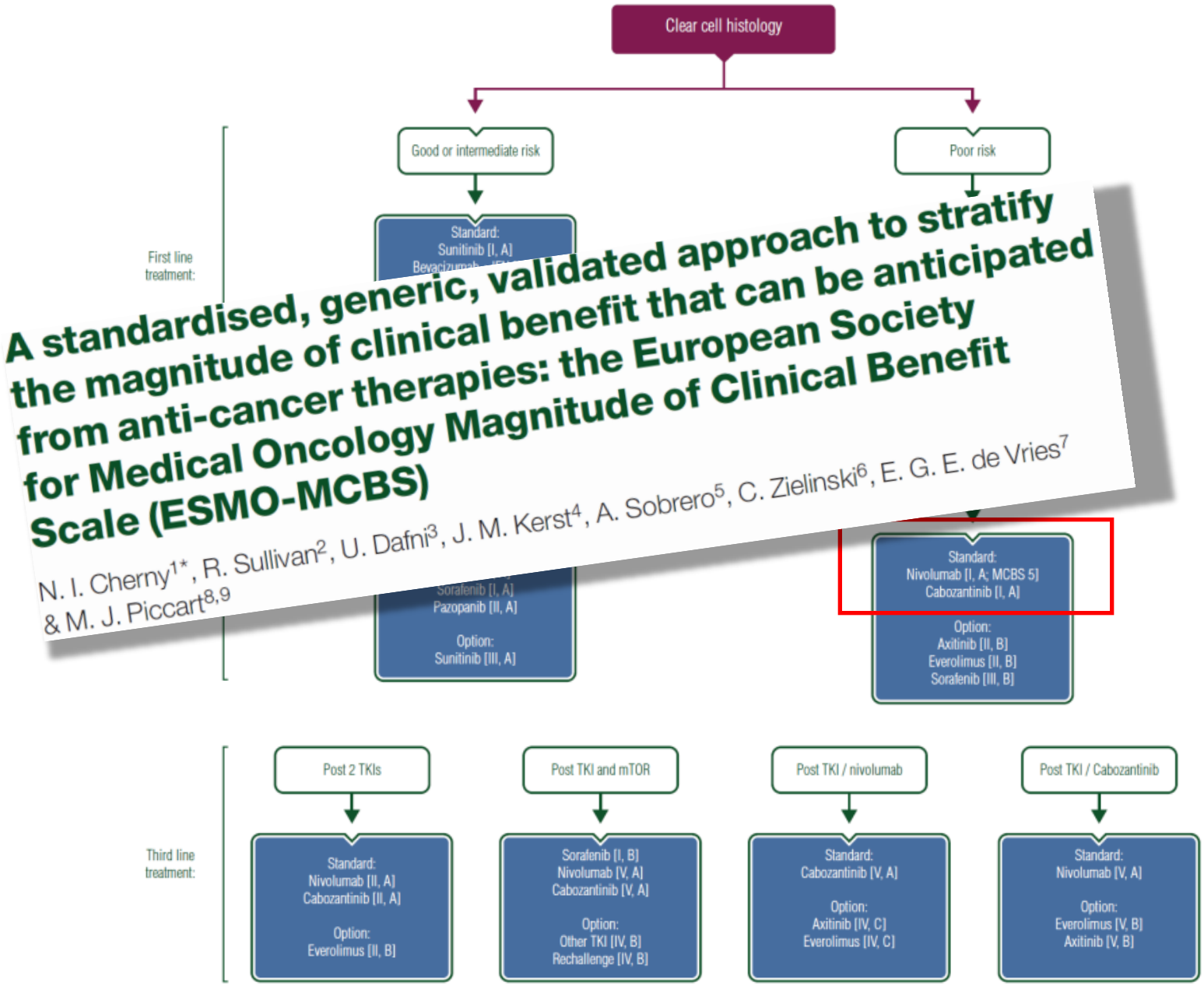
Grade de Recommandation

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

ESMO Guidelines Committee, October 2015, latest revision October 2017

Nivolumab & Guidelines (ESMO 2016)



A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Cherny[1*], R. Sullivan[2], U. Dafni[3], J. M. Kerst[4], A. Sobrero[5], C. Zielinski[6], E. G. E. de Vries[7] & M. J. Piccart[8,9]

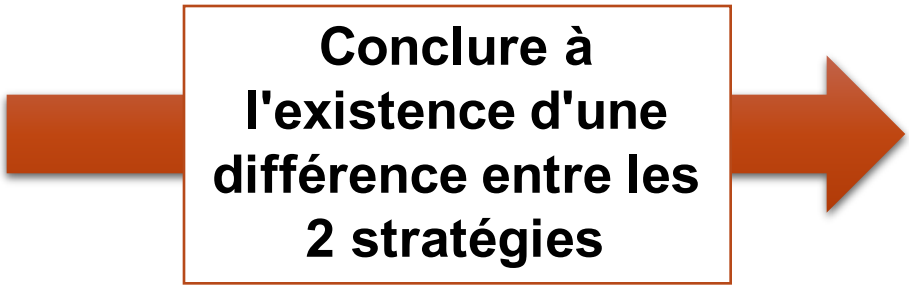
Essai randomisé comparatif

Comparaison de 2 traitements

Traitement A

VS

Traitement B



Définition d'un nouveau standard

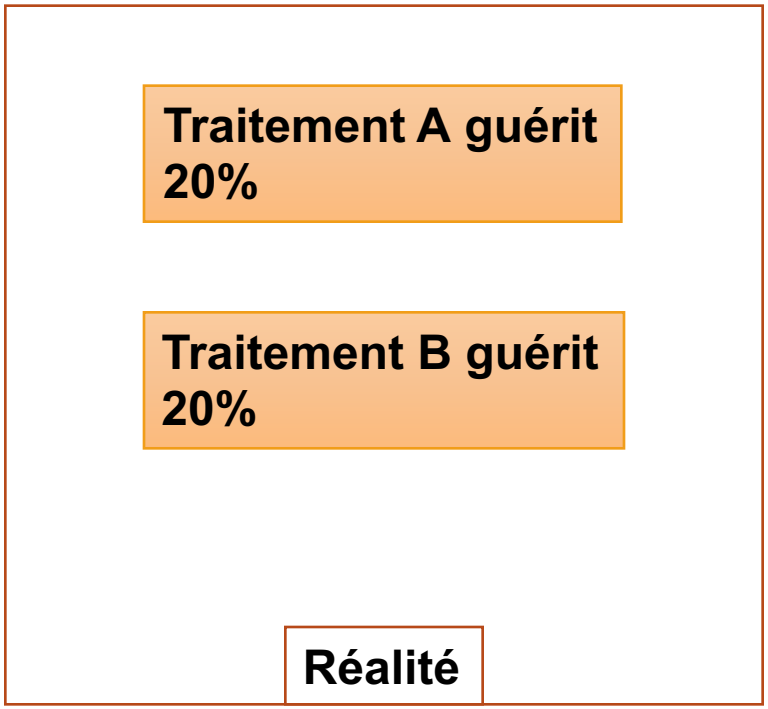
La conclusion doit être conforme à la réalité mais elle se base uniquement sur l'observé

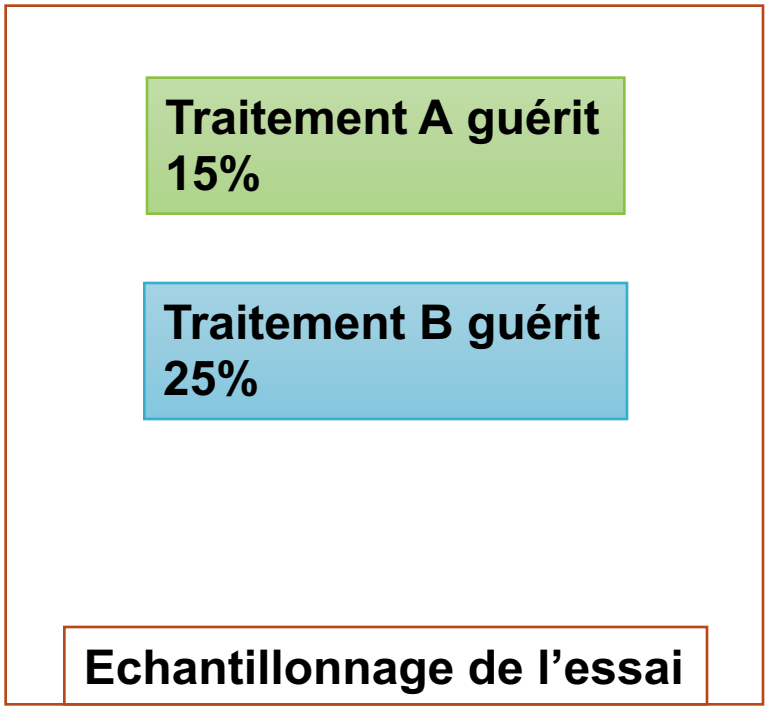
Ne pas se tromper

- Deux risques d'erreur
  - Risque alpha et Risque bêta

Ne pas se tromper

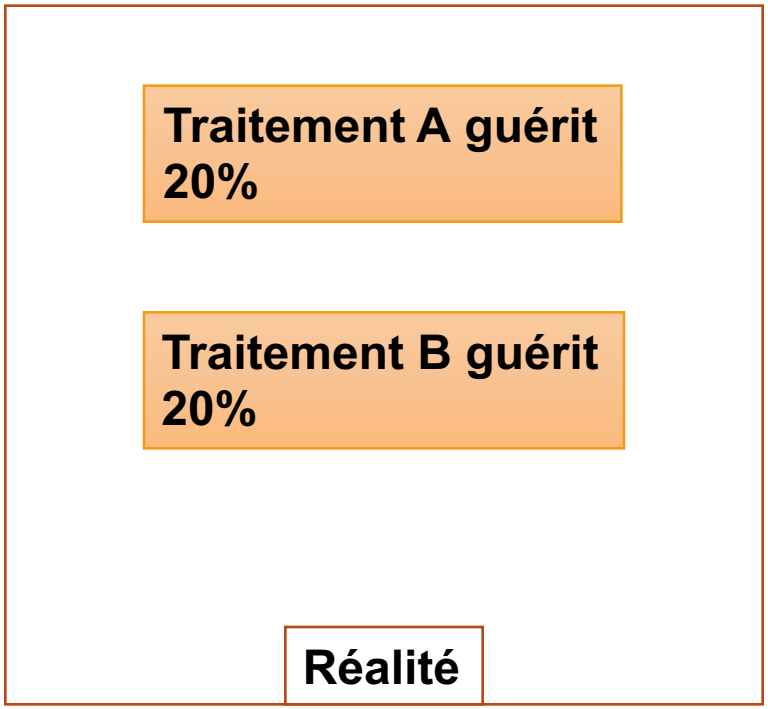
- Deux risques d'erreur
  - Risque **alpha** et Risque bêta

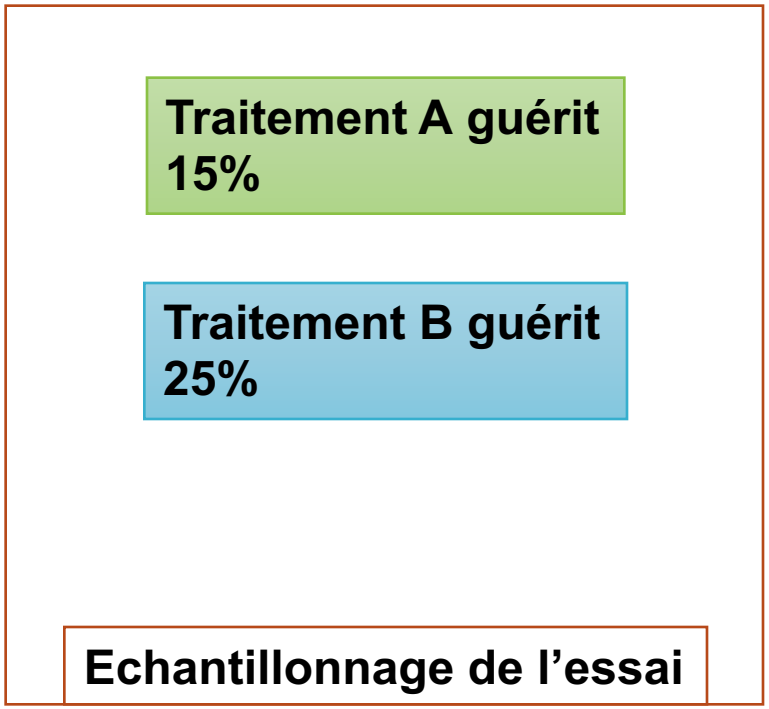




Ne pas se tromper

- Deux risques d'erreur
  - Risque **alpha** et Risque bêta
  - **Conclure à l'existence d'une différence qui n'existe pas en réalité : faux positif**

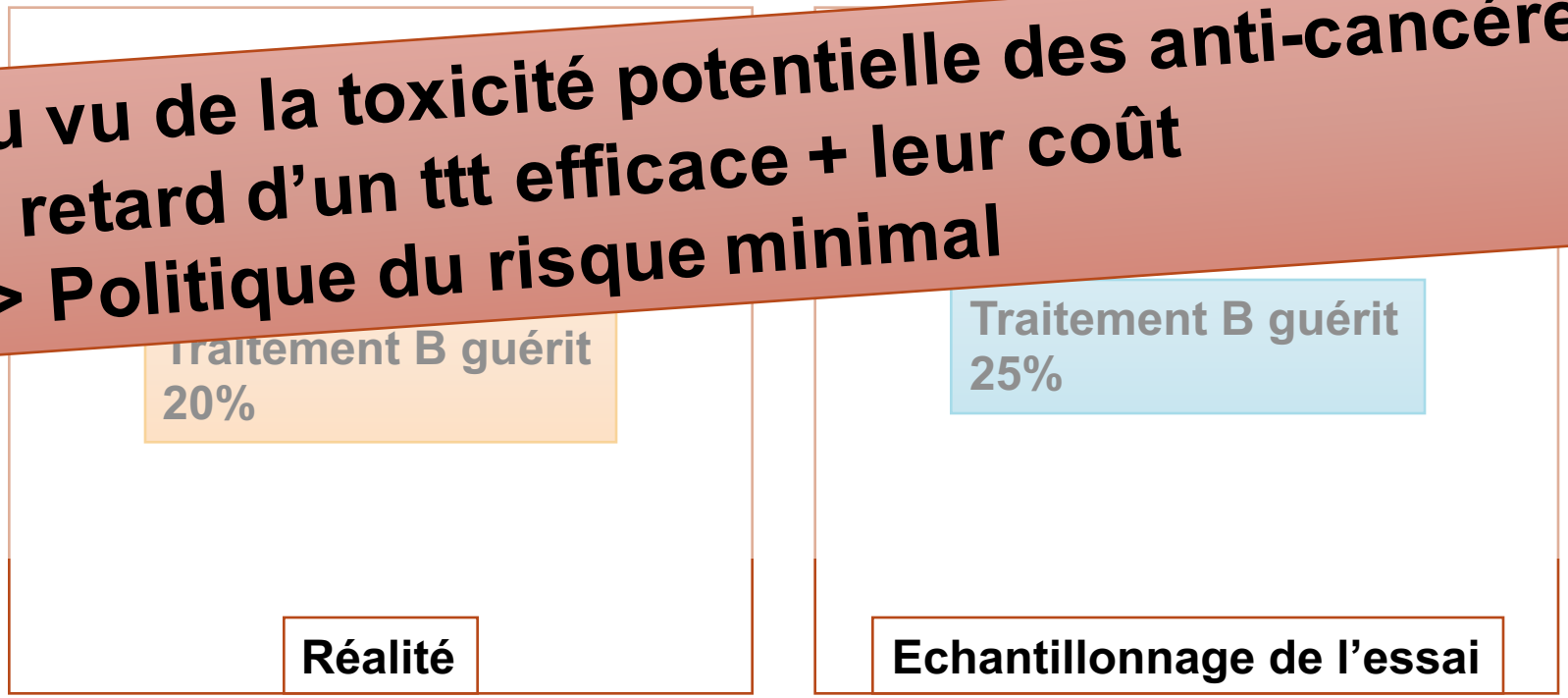




Ne pas se tromper

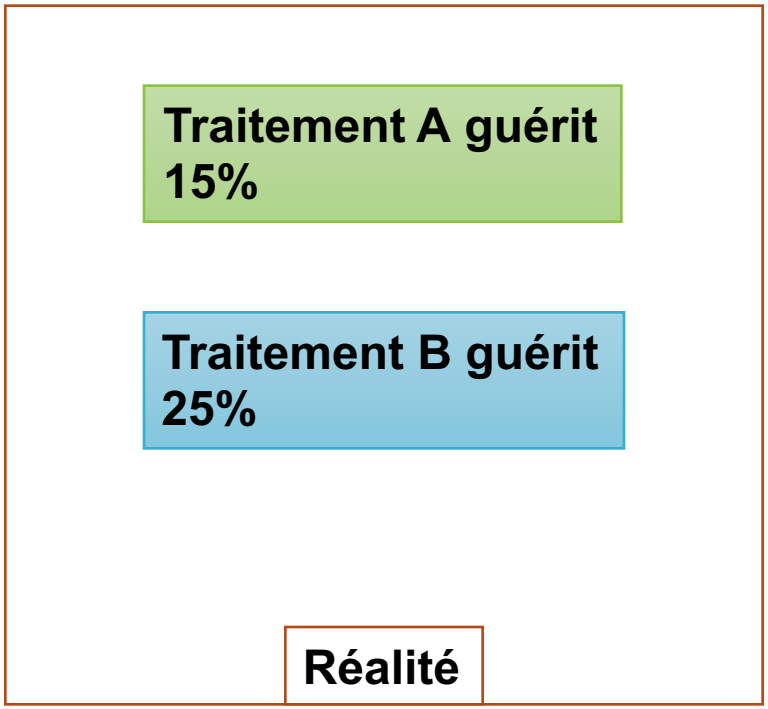
- Deux risques d'erreur
  - Risque **alpha** et Risque bêta
  - **Conclure à l'existence d'une différence qui n'existe pas en réalité : faux positif**

Au vu de la toxicité potentielle des anti-cancéreux
+ retard d'un ttt efficace + leur coût
=> Politique du risque minimal



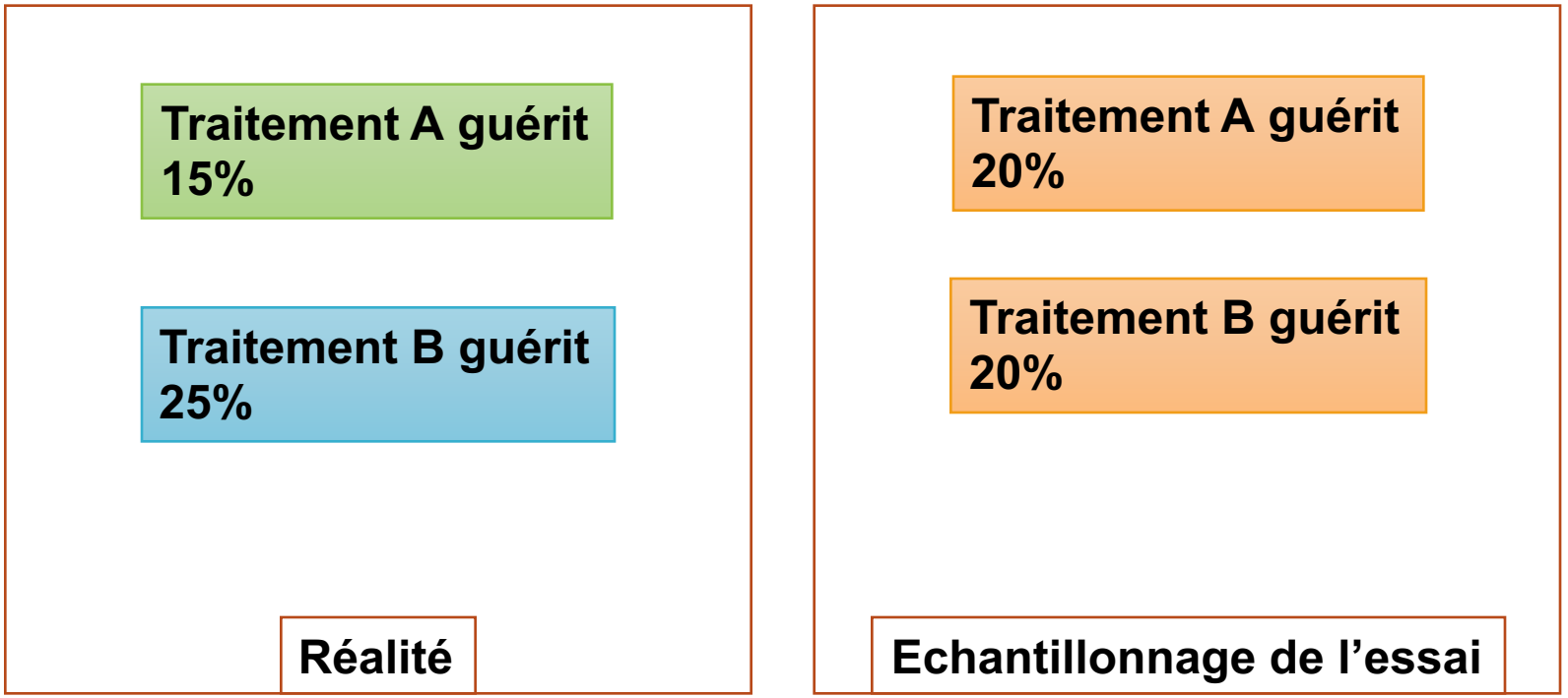
Ne pas se tromper

- Deux risques d'erreur
  - Risque alpha et Risque **bêta**



Ne pas se tromper

- Deux risques d'erreur
  - Risque alpha et Risque **bêta**
- **Ne pas conclure à une différence qui existe pourtant en réalité : faux négatif**



Ne pas se tromper

- Risques d'erreur statistiques
  - Risque **alpha** : risque de conclure à une différence qui n'existe pas

  => considérer qu'un traitement est efficace alors qu'il ne l'est pas
  - Risque bêta : risque de ne pas mettre en évidence une différence qui existe réellement

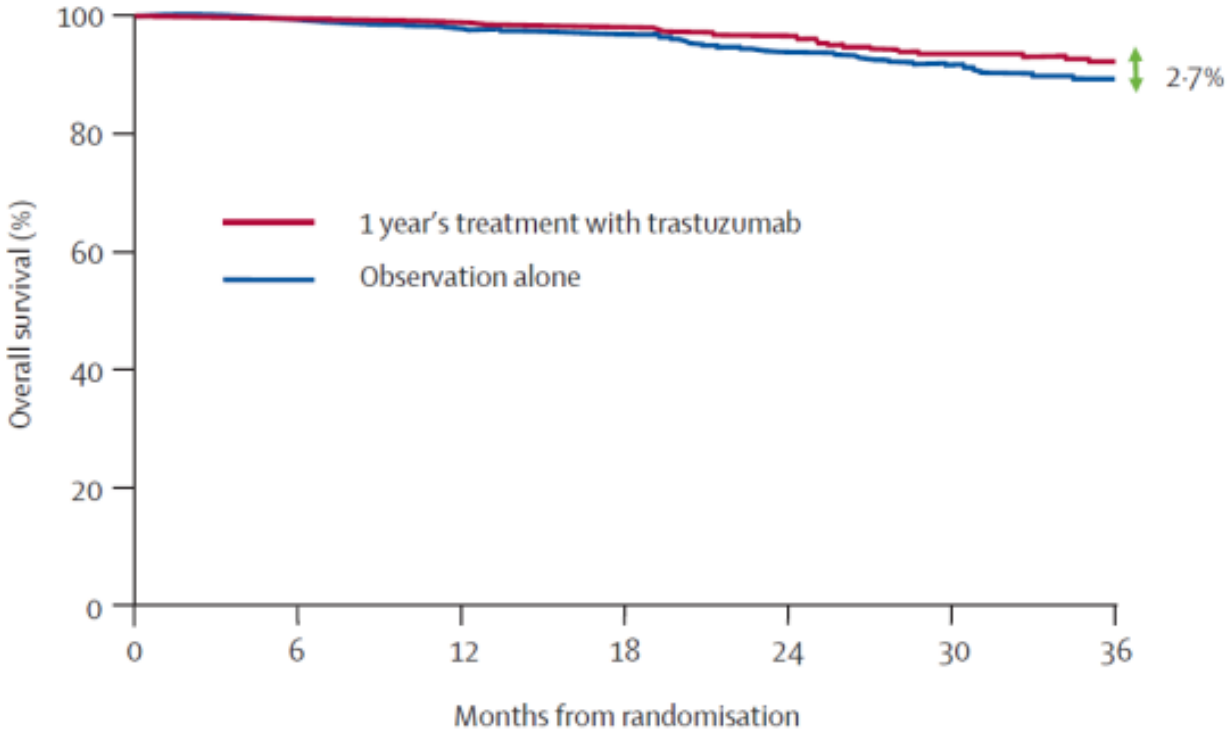
  => Passer à coté d'un traitement efficace
  - **Puissance** : 1 - bêta : probabilité de mettre en évidence une différence qui existe réellement

  => montrer l'efficacité d'un traitement réellement efficace

Test statistique

- Moyen qui autorise à conclure à l'existence d'une différence que si le risque de commettre une erreur est faible
- Risque d'erreur faible = 5% (en général)
  - seuil de décision
- **Contrôle** du risque alpha
  - mais le risque d'erreurs alpha **persiste**
  - 100 essais avec un traitement sans efficacité
    - conclusion à tort à l'efficacité dans 5 essais

Risque Absolu vs Relatif



Numbers at risk							
Trastuzumab	1703	1627	1498	1190	794	407	146
Observation	1698	1608	1453	1097	711	366	139

The unadjusted HR for the risk of death in the trastuzumab group compared with observation alone was 0.66 (.47–0.91; p=0.0115 by the log rank test); which corresponds with an absolute overall survival benefit of 2.7% (92.4% *vs* 89.7%) at 3 years

HERA Trial Lancet 2007

Critères de qualité d'un essai de phase III

- Méthodologie +++
- Pertinence de la question posée
- Critères de jugement / Objectifs
- Puissance statistique
- Qualité randomisation / stratification
- Qualité analyse
- Conclusions / Contexte

Fiabilité : jugement méthodologique

Valeur médicale : question / resultat / contexte

Sommaire

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Utilité d'une phase 3

- **Grand nombre de patients**
- **Temps**
- **Coût financier**

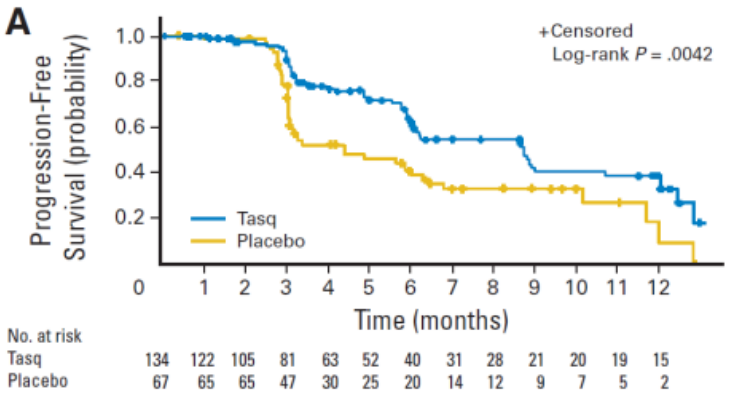
Utilité d'une phase 3

- **Grand nombre de patients**
- **Temps**
- **Coût financier**

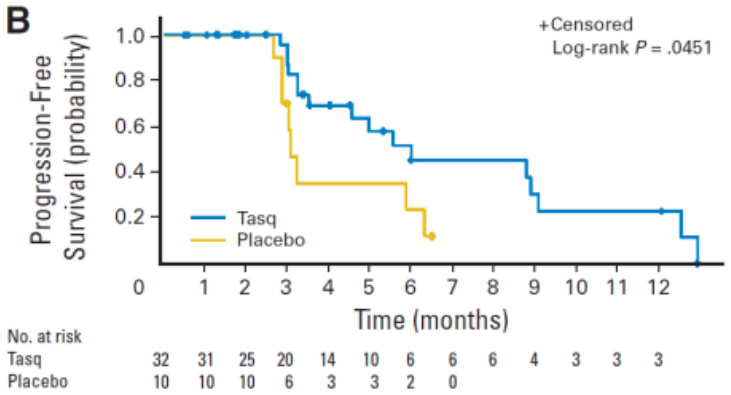
- **Une bonne phase 2 ne serait elle pas suffisante ?**

Tasquinimod phase 2

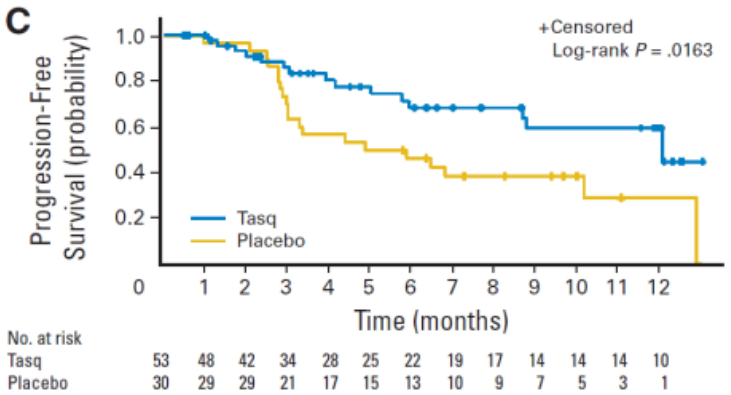
HR 0.49; 95% CI, 0.36 to 0.67
P <0 .001



All patients



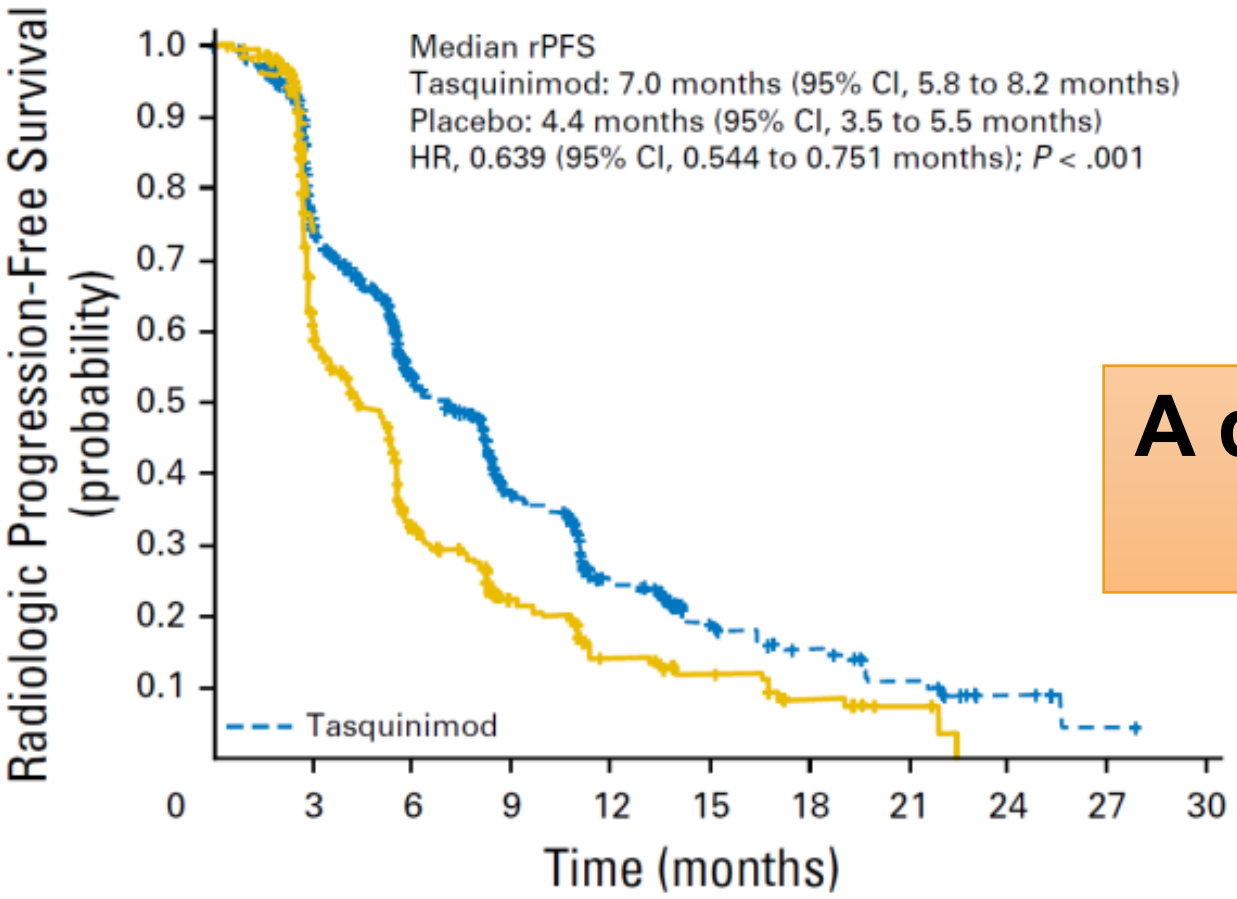
Visceral Mets



Bone Mets

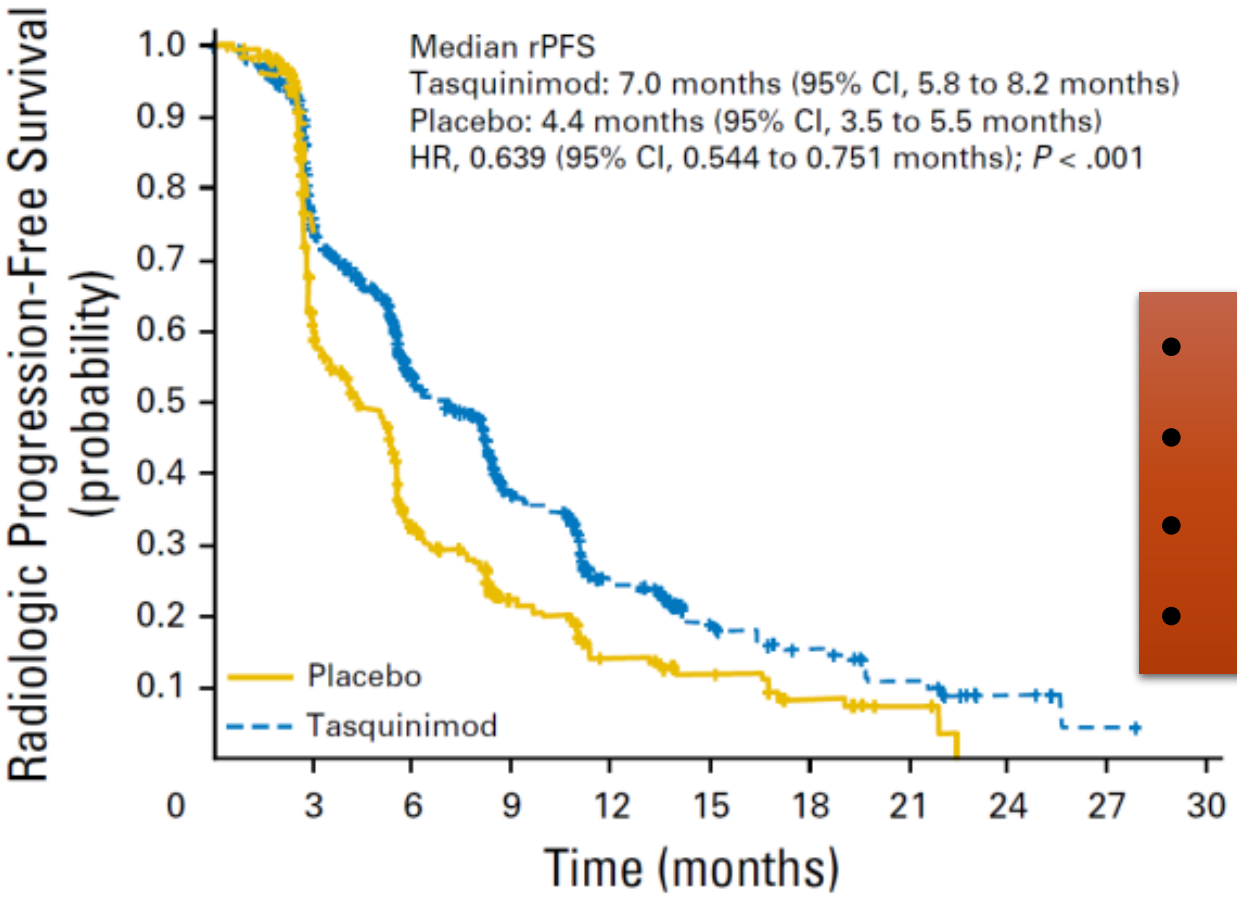
Pili JCO 2011

Tasquinimod phase 3



A quand AMM ?

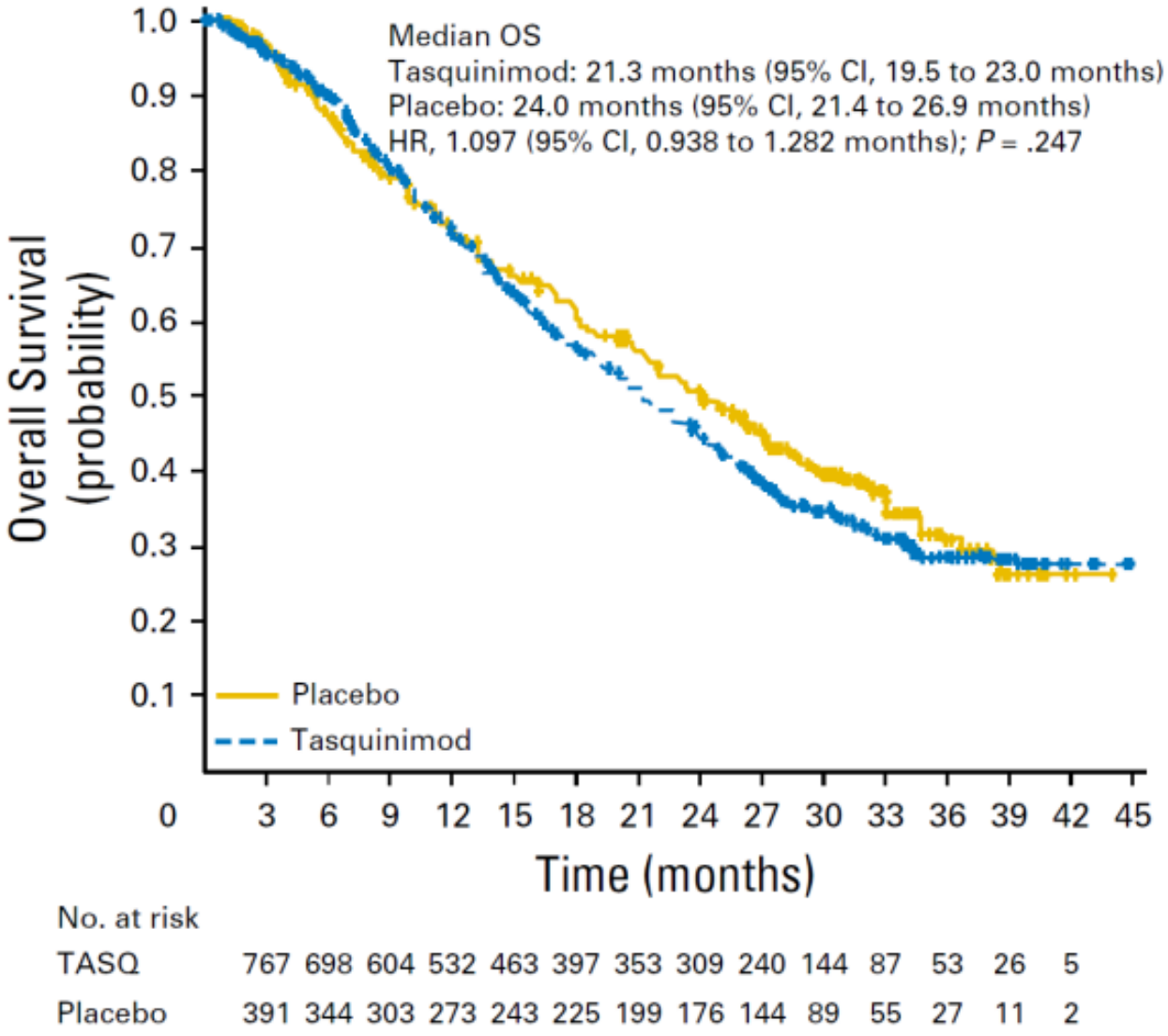
Tasquinimod phase 3



- **Relevance**
- **Activité/Safety**
- **Amplitude**
- **Comparateur**

Sternberg JCO 2016

Tasquinimod phase 3



- **OS**
- **MOA**

Sternberg JCO 2016

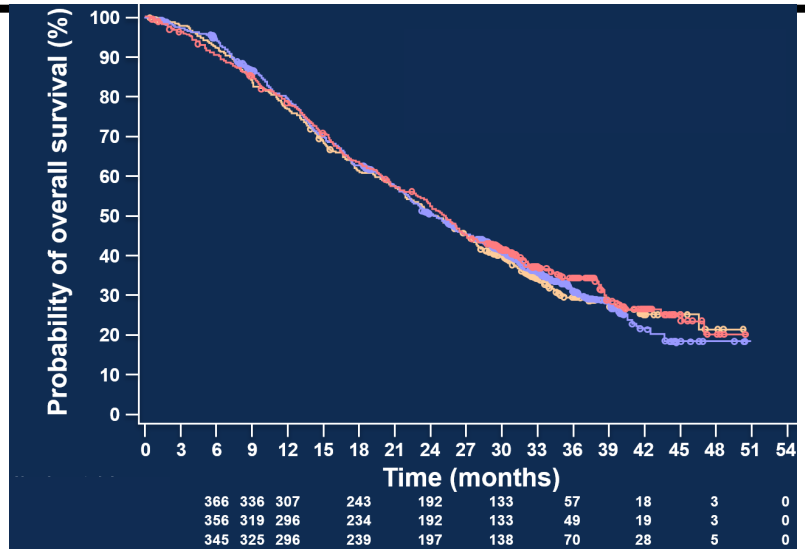
De l'importance d'une phase 3

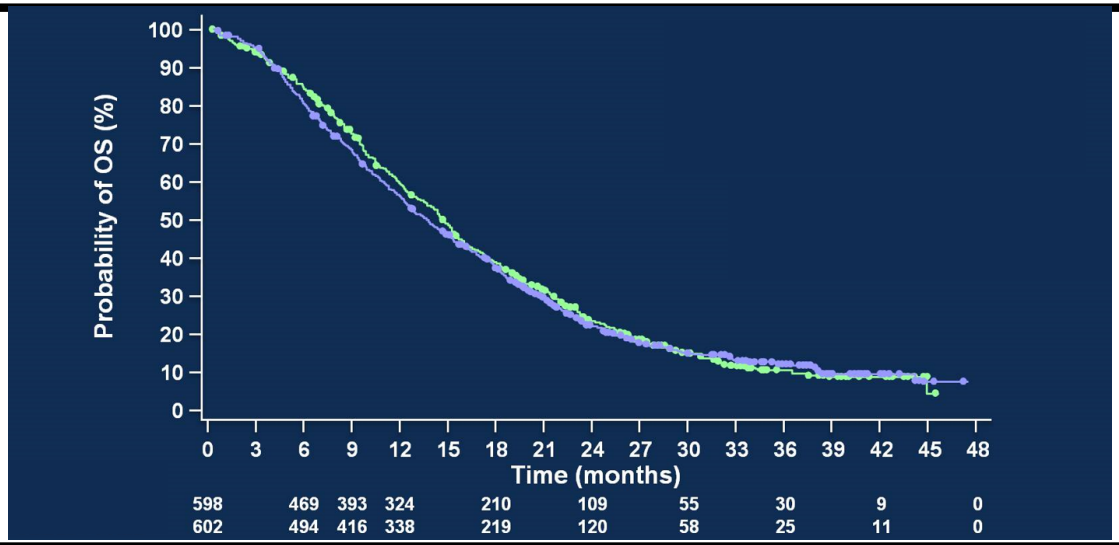
- **Phase 2 randomisée positive => Echec en phase 3**
  - **Cabozantinib prostate**
  - **Tasquinimod prostate**

- **Lenvatinib (rein) positive ph 2 => phase 3 en cours**

Cabazitaxel Prostate

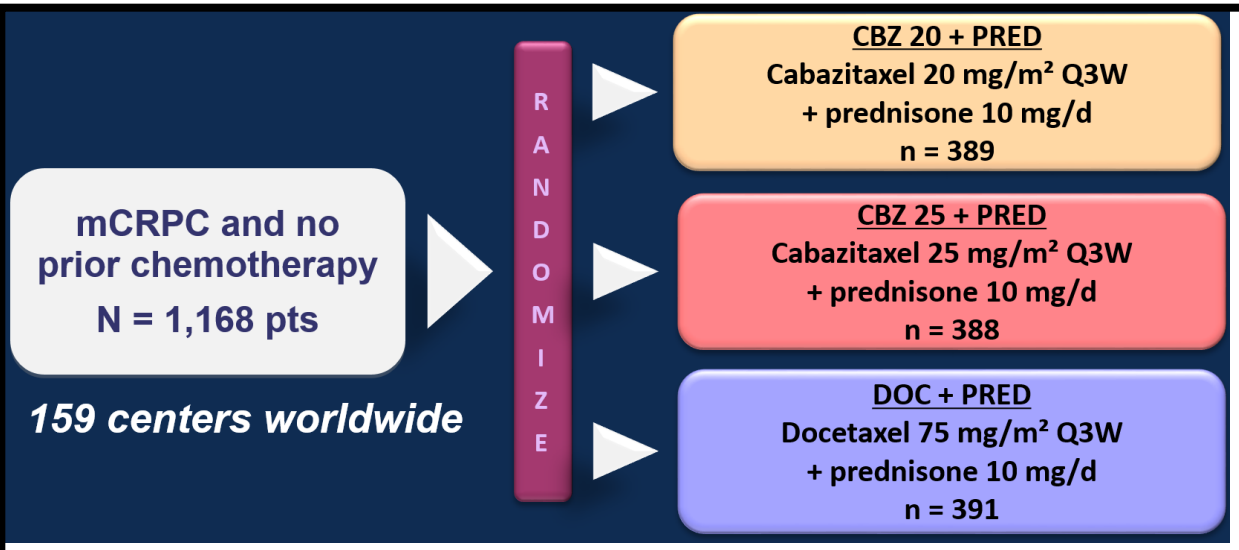
Survie Globale : quelle est étude positive ?





Taxanes : Firstana & Proselica

Trial designs : supériorité et non-infériorité



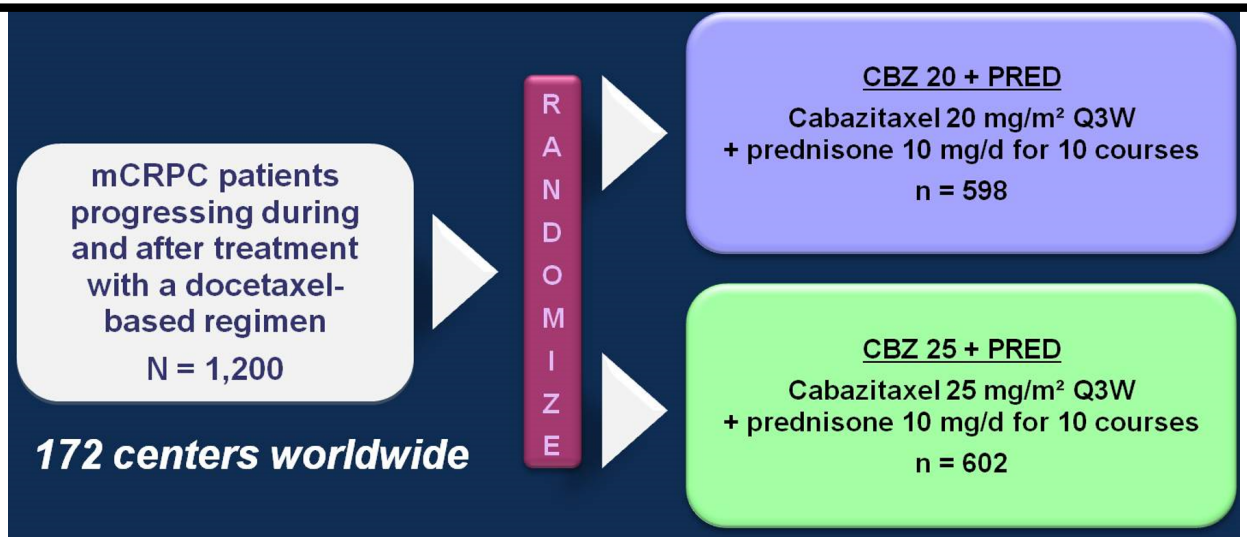
FIRSTANA

Phase 3
Etude de supériorité
Survie Globale
Chimio naïfs

Sartor ASCO 2016

PROSELICA

Phase 3
Etude de non-infériorité
Survie Globale
Post Docetaxel



De Bono ASCO 2016

Taxanes : Firstana & Proselica

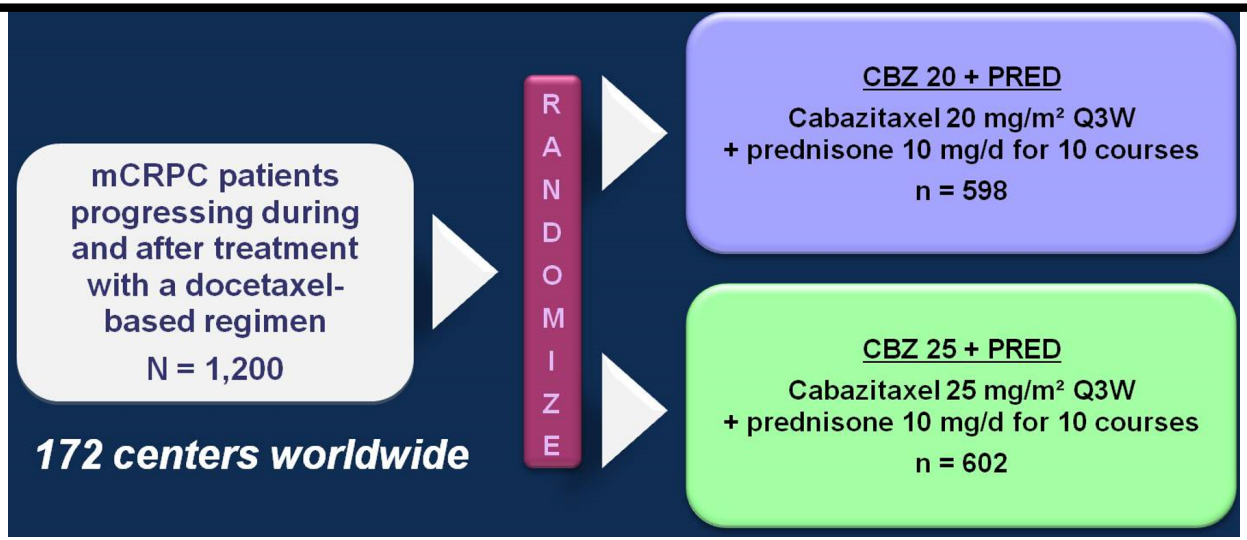
Trial designs

The sample size for this study was determined to test **whether C20 could maintain at least 50% of the OS benefit of C25** that had been demonstrated in the registrational phase III TROPIC study and was based on recommendations provided as part of a postmarketing requirement. In TROPIC, C25 reduced the relative risk of death by 30%, compared with mitoxantrone (hazard ratio [HR], 0.70; 95% CI, 0.59 to 0.83; P < 0.001).

The objective of this study was to test whether treatment with C20 leads to a ≥ **15%** reduction in risk of death compared with the results reported with mitoxantrone in TROPIC (ie, HR ≤ 0.85). On the basis of these assumptions, the **noninferiority margin of the HR for C20 versus C25 was defined as 1.214** in this trial (HR of 0.85 divided by HR of 0.70).

PROSELICA

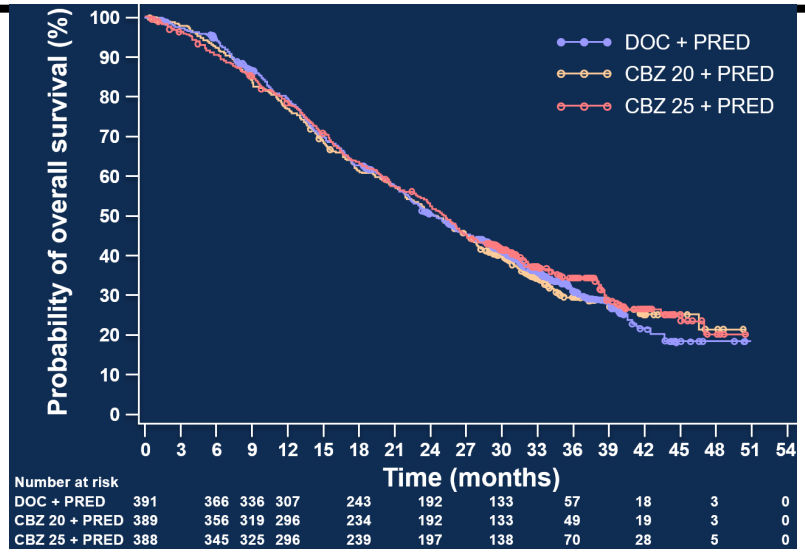
Phase 3
Etude de non-infériorité
Survie Globale
Post Docetaxel



De Bono ASCO 2016

Taxanes : Firstana & Proselica

Survie Globale



FIRSTANA

Négative

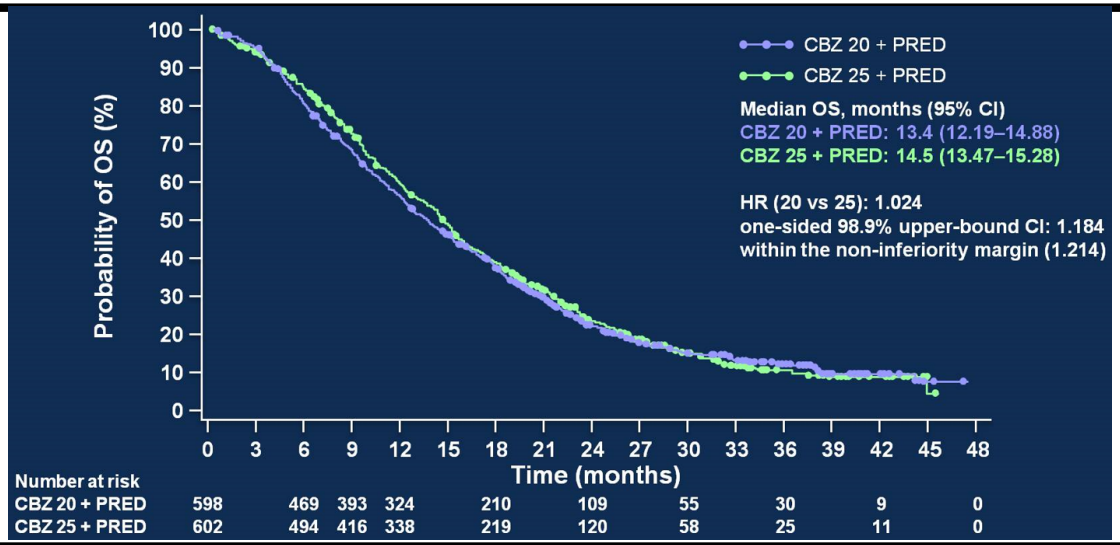
cabazitaxel n'est pas supérieur au docetaxel

Sartor ASCO 2016

PROSELICA

Positive

20mg/m2 est non-inférieur à 25mg/m2

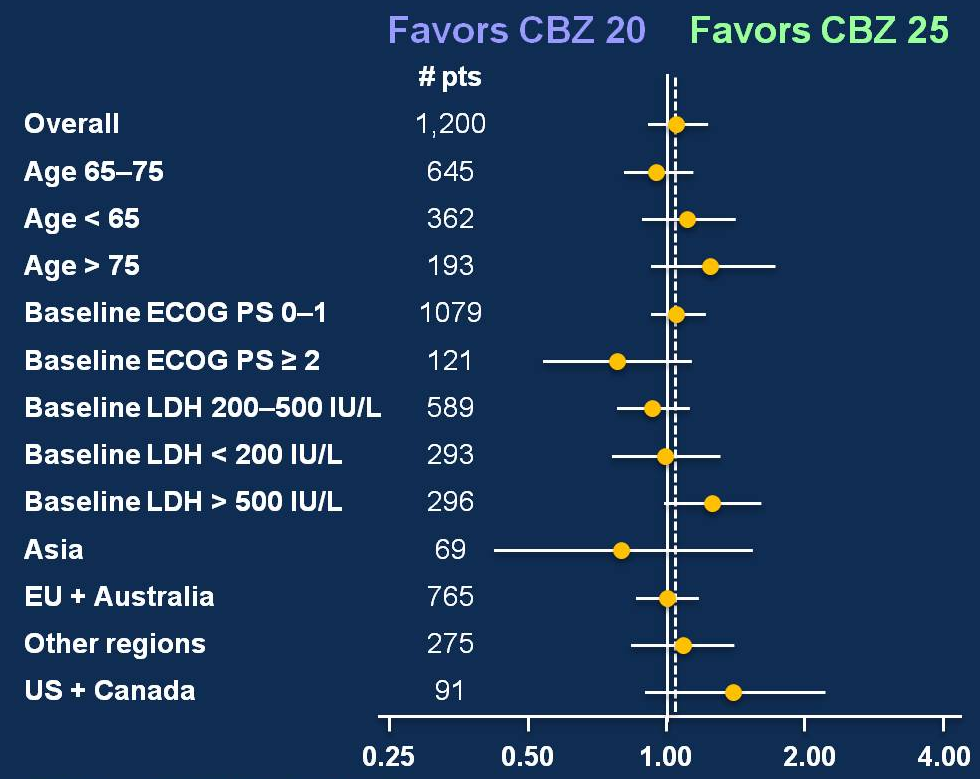


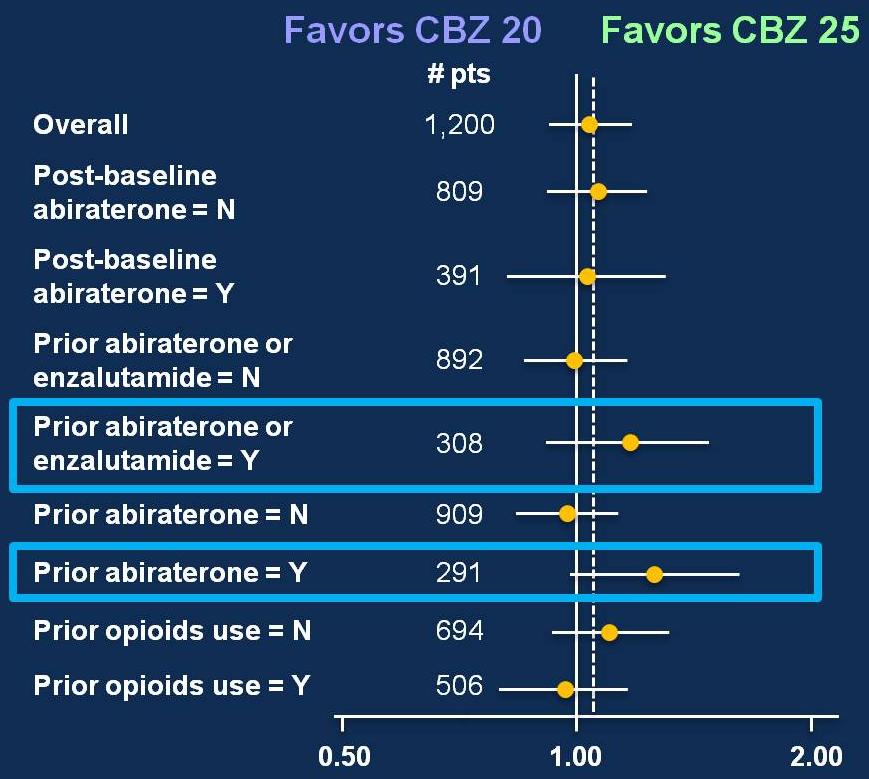
De Bono ASCO 2016

Pour patient mCRPC 2017 (1)

Qui a reçu abiraterone / enzalutamide

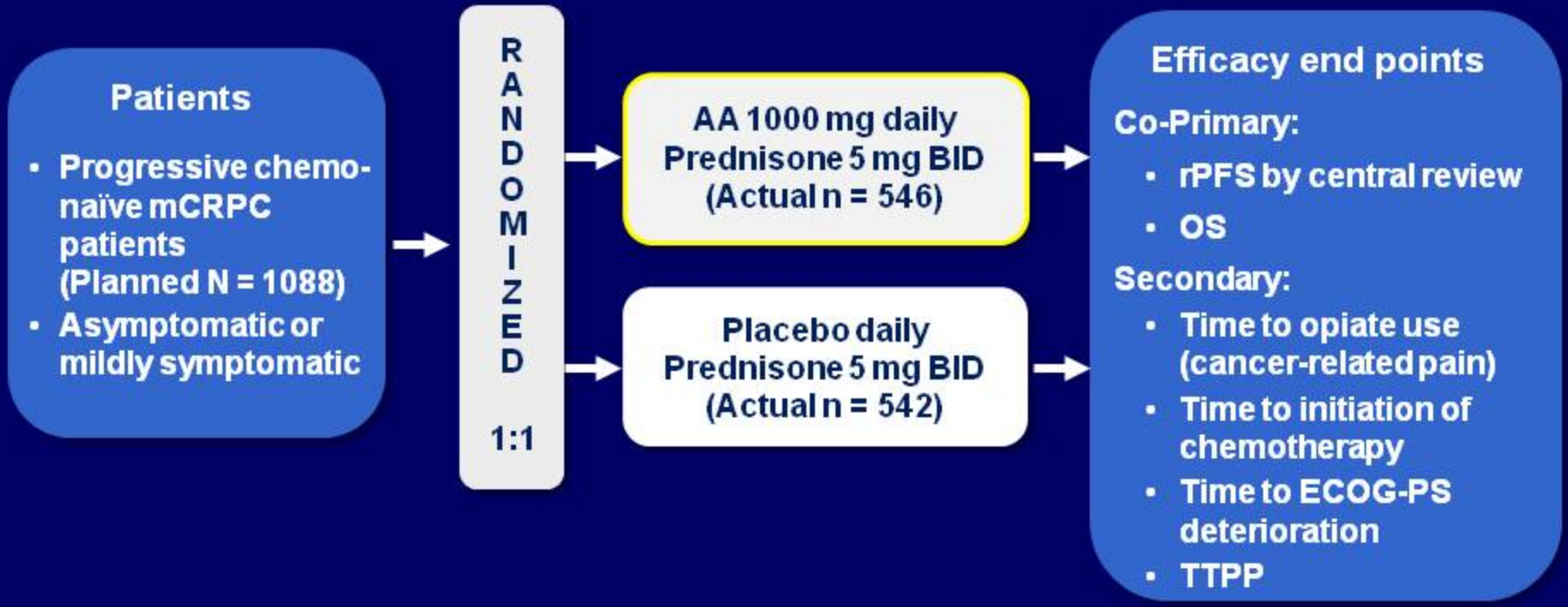
PROSELICA: Overall Survival by Subgroup[a]





[a] CBZ 20 vs CBZ 25 HR with 95% CI

Overall Study Design of COU-AA-302



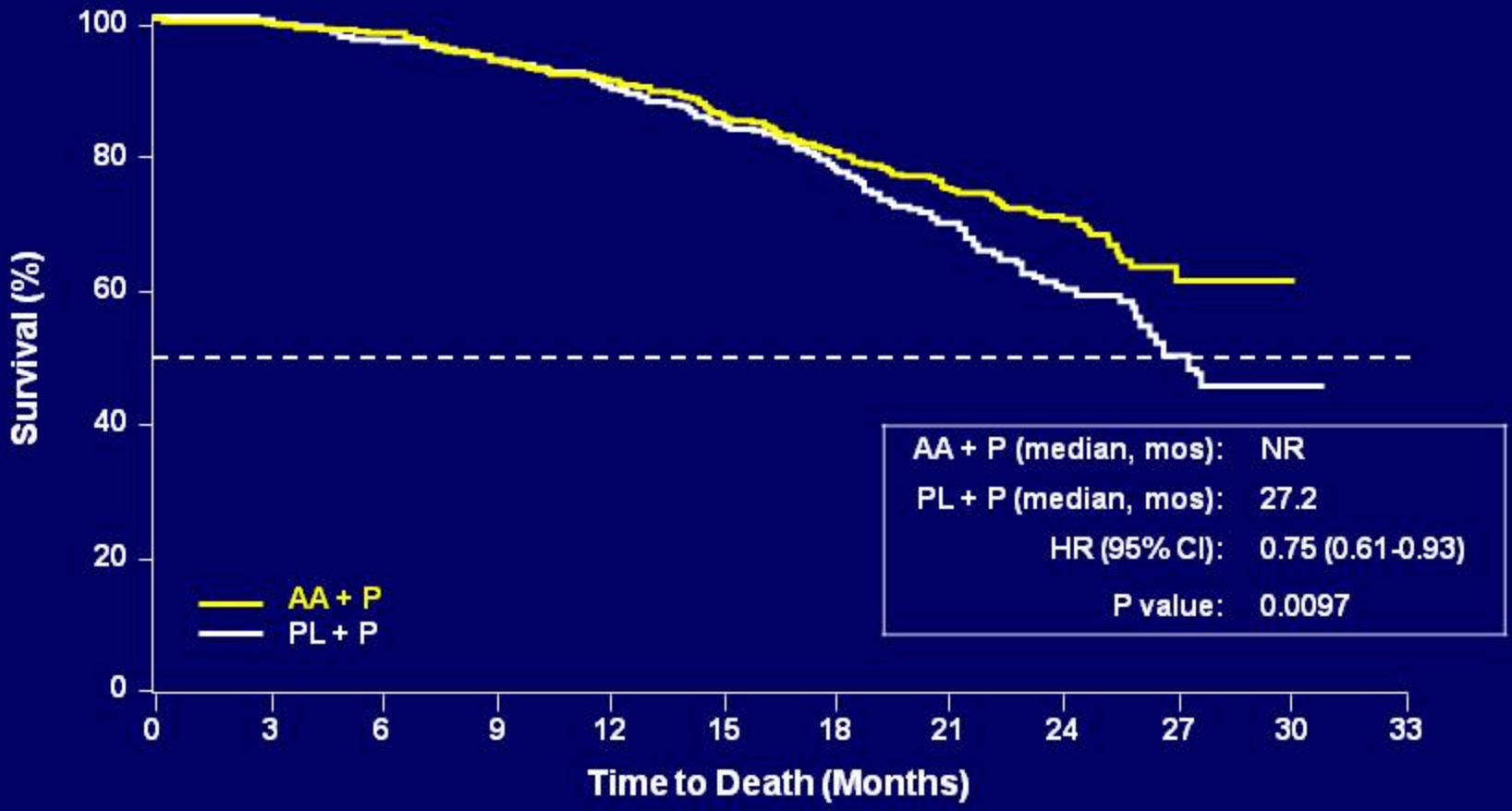
- Phase 3 multicenter, randomized, double-blind, placebo-controlled study conducted at 151 sites in 12 countries; USA, Europe, Australia, Canada
- Stratification by ECOG performance status 0 vs 1

COU-AA-302 Statistical Plan

Overall Assumption	rPFS	OS
α	0.01	0.04
Power	91%	85%
HR	0.67	0.80
Expected events	378	773

Co-Primary

OS Primary End Point



AA	546	538	524	503	482	452	412	258	120	27	0	0
PL	542	534	509	493	465	437	387	237	106	25	2	0

COU-AA-302 Statistical Plan

Overall Assumption	rPFS	OS
α	0.01	0.04
Power	91%	85%
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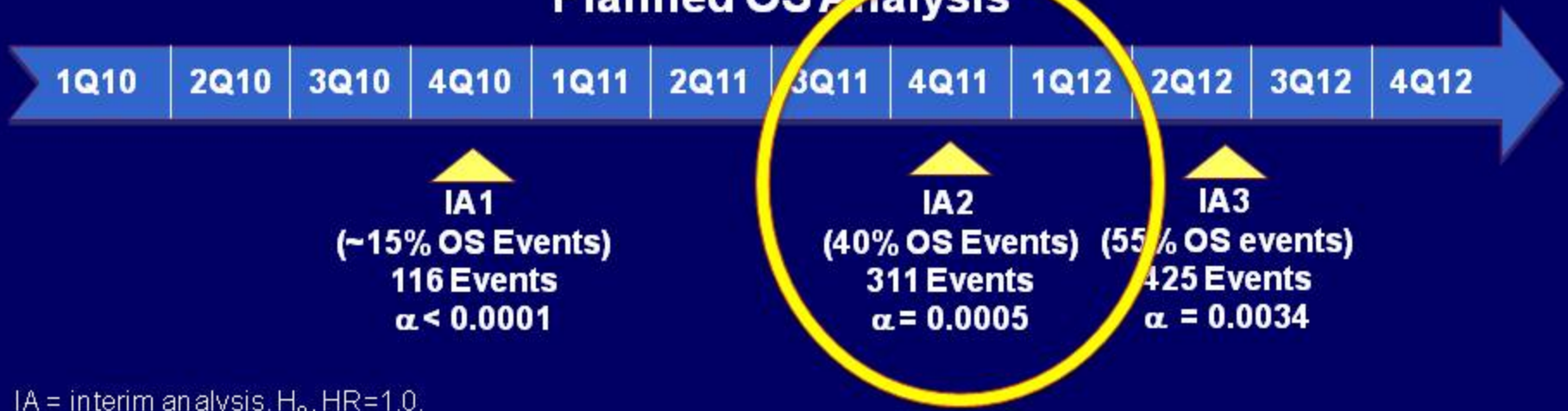
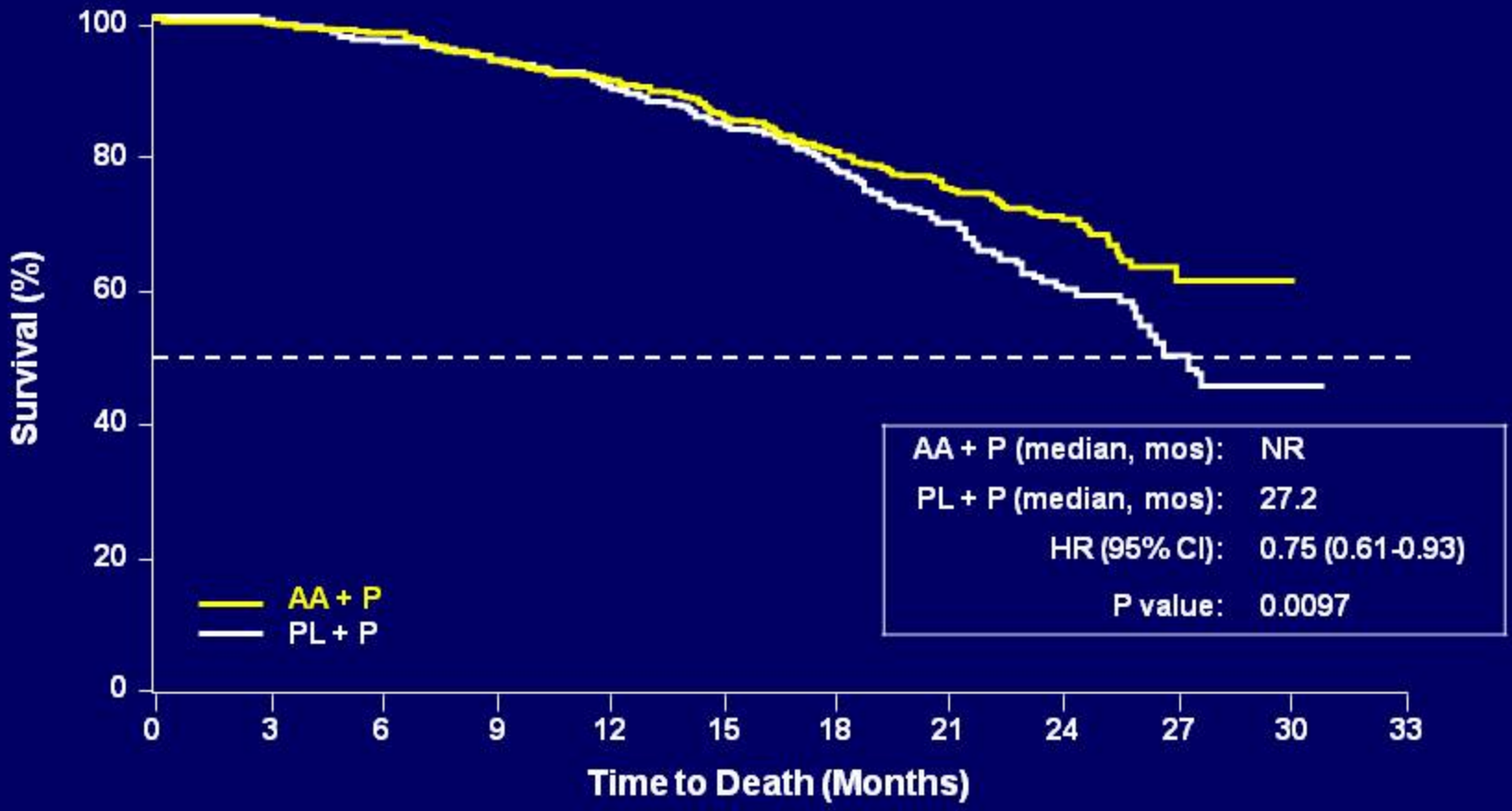
Co-Primary

Planned OS Analysis



IA = interim analysis. H_0, HR=1.0.

Strong Trend in OS Primary End Point

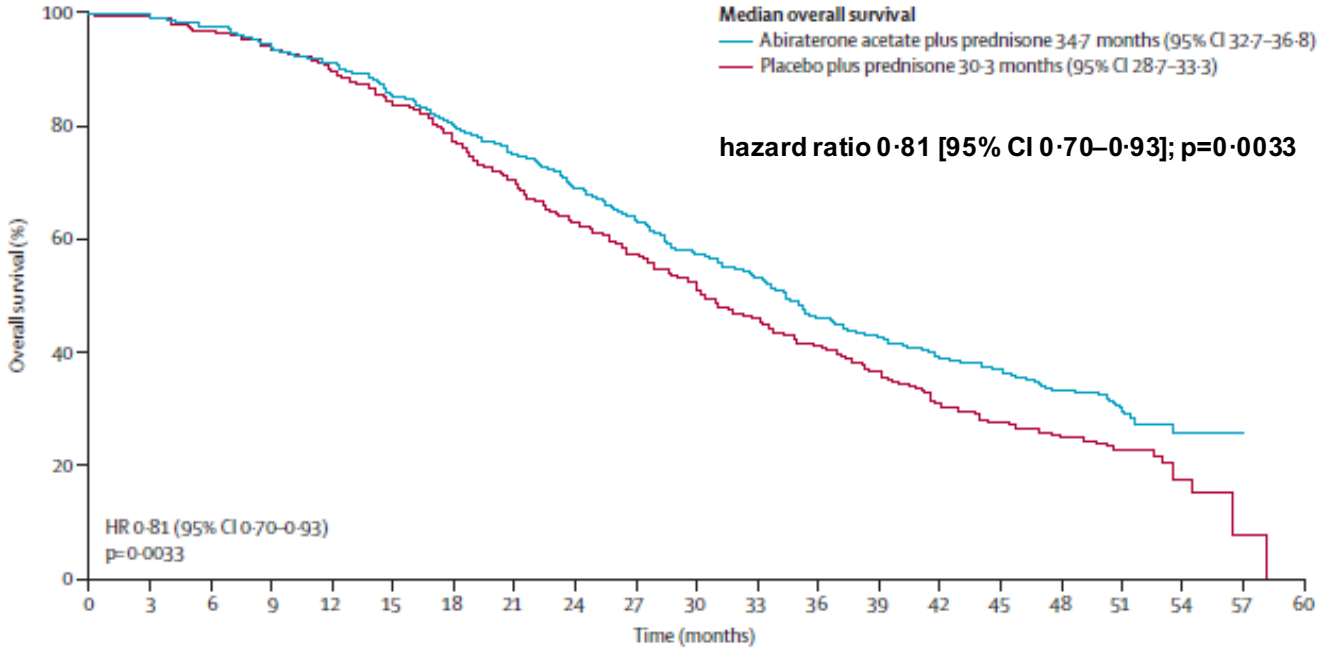


AA	546	538	524	503	482	452	412	258	120	27	0	0
PL	542	534	509	493	465	437	387	237	106	25	2	0

Data cutoff 12/20/2011.

Pre-specified significance level by O'Brien-Fleming Boundary = 0.0008.

COUAA302 final OS

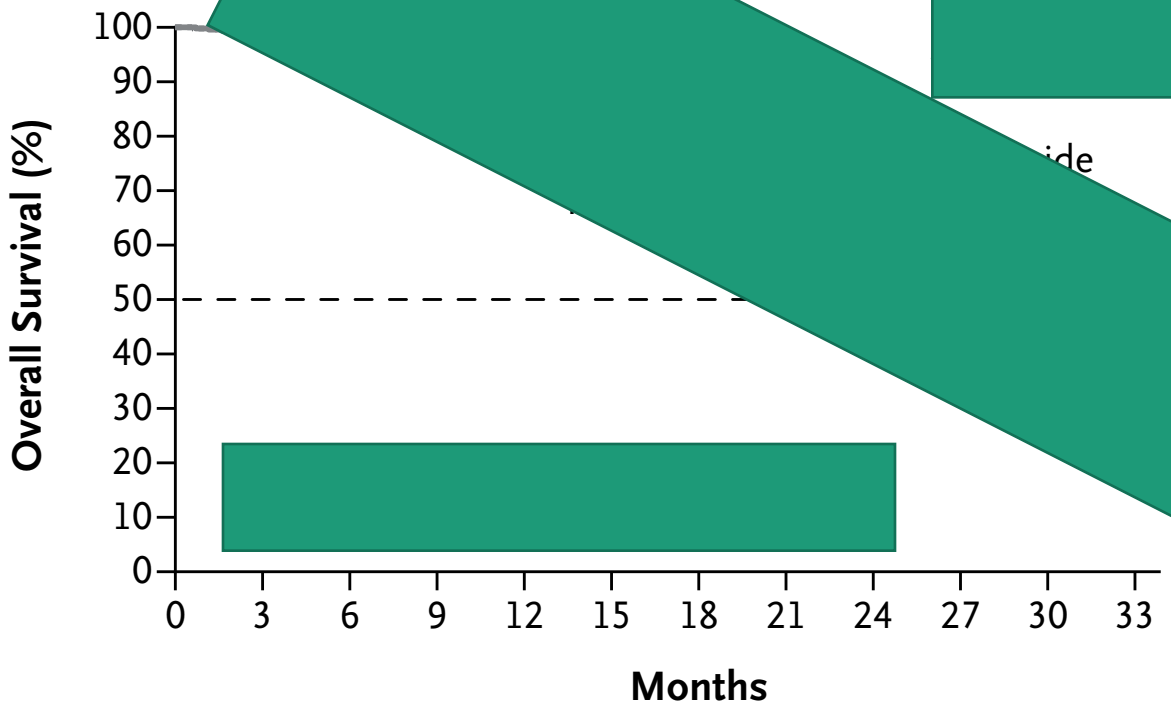


	Number of expected deaths (% of expected)	HR (95% CI)	p value
Interim analysis 1*	98 (13%)	1·08 (0·73–1·61)	0·69
Interim analysis 2†	333 (43%)	0·75 (0·61–0·93)	0·0097
Interim analysis 3‡	434 (56%)	0·79 (0·66–0·95)	0·015
Final analysis§	741 (96%)	0·81 (0·70–0·93)	0·0033

HR=hazard ratio. *Efficacy boundary HR 0·34, nominal significance level α<0·0001. †Efficacy boundary HR 0·67, nominal significance level α=0·0008. ‡Efficacy boundary HR 0·75, nominal significance level α=0·0035. §Efficacy boundary HR 0·86, nominal significance level α=0·038.

Ryan et al. Lancet Oncol 2015

PREVAIL OS : Superiority trial



No. at Risk

Enzalutamide	872	863	850	824	797	745	566	395	244	128	33	2
Placebo	845	835	781	744	701	644	484	328	213	102	27	2

Beer et al.
NEJM 2014

Phase 3 positive = AMM ?

- Exemple de tivozanib
- mRCC

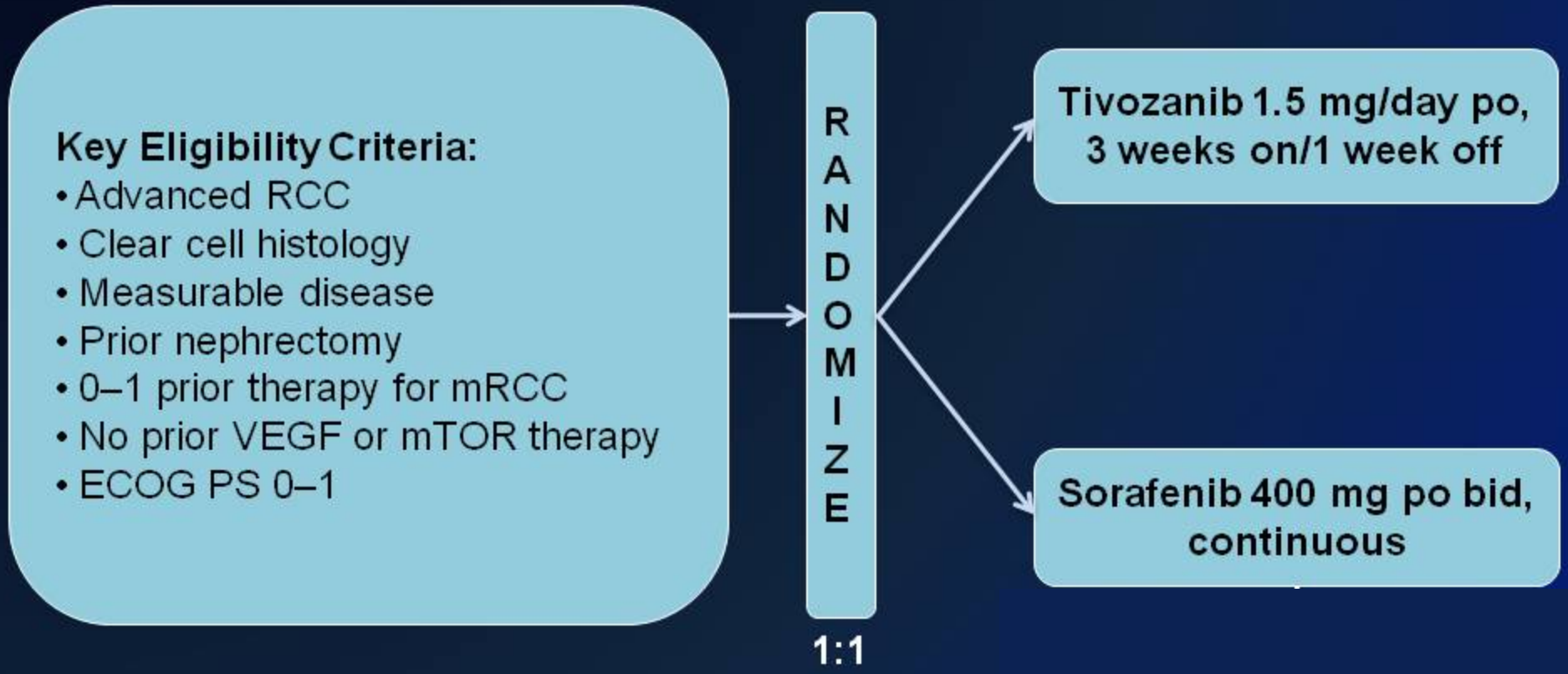
Abstract No. 4501

Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell carcinoma: Results from a Phase III randomized, open-label, multicenter trial

R. Motzer, D. Nosov, T. Eisen, I. Bondarenko, V. Lesovoy, O. Lipatov, P. Tomczak, O. Lyulko, A. Alyasova, M. Harza, M. Kogan, B.Y. Alexeev, C.N. Sternberg, C. Szczylik, J. Zhang, A. Strahs, B. Esteves, W. Slichenmyer, A. Berkenblit, T.E. Hutson, and the TIVO-1 Study Group

ASCO 2012

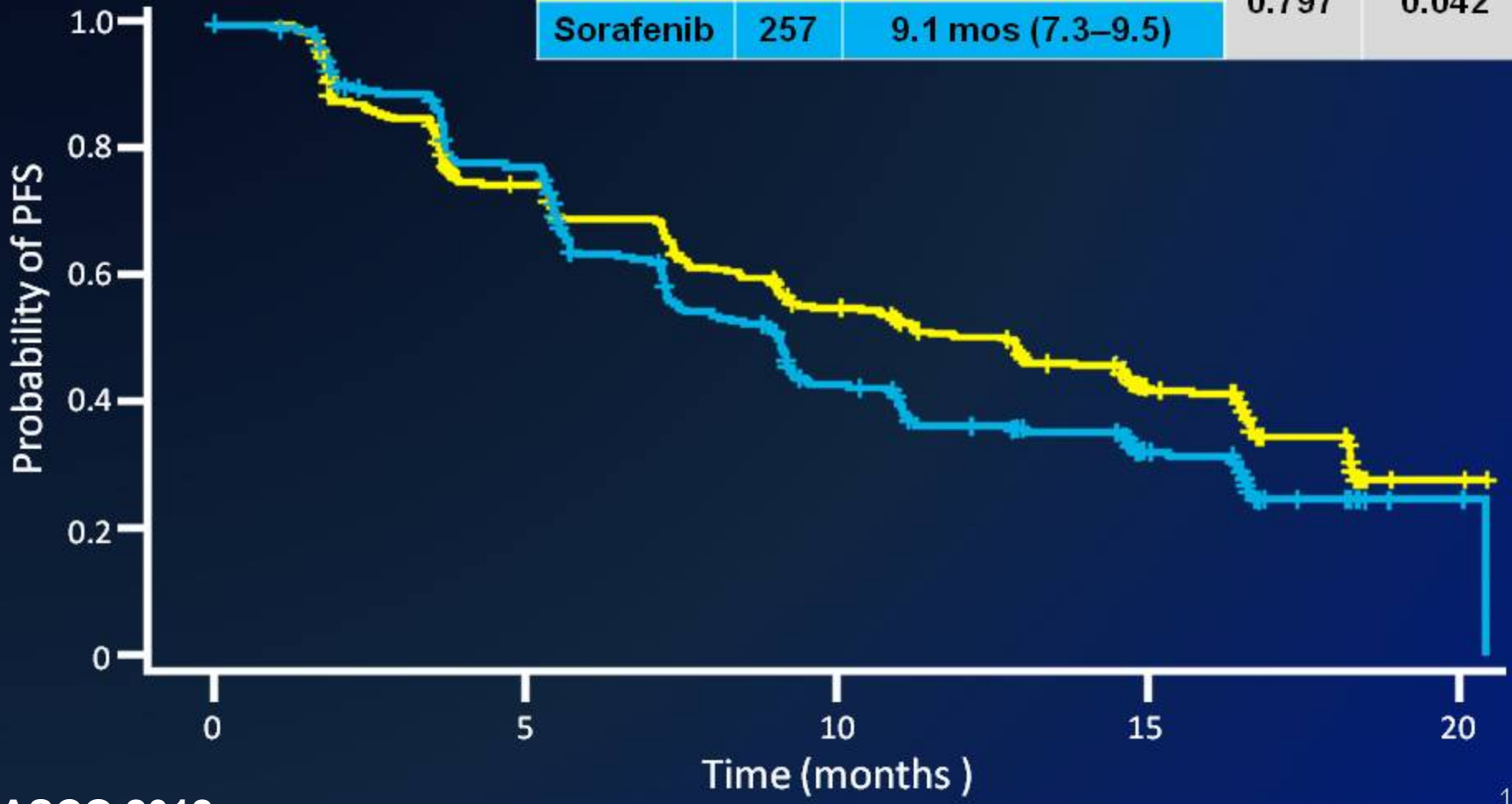
TIVO-1: Phase III superiority study of tivozanib vs sorafenib as first-line targeted therapy for mRCC



Stratification Factors:
- Geographic region
- Prior treatments for mRCC
- # of metastatic lesions

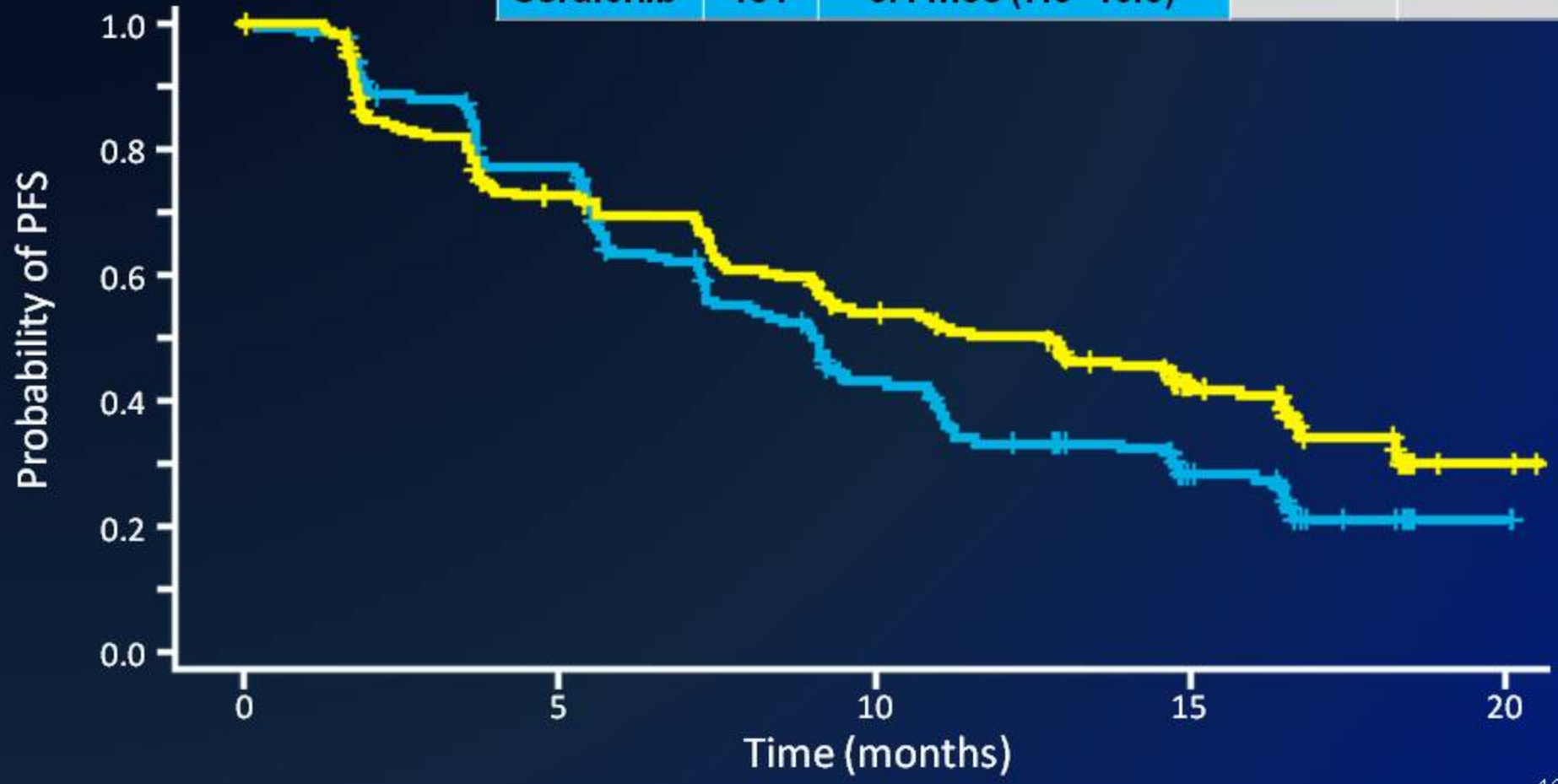
Primary endpoint: Progression-free survival (independent review)

	N	Median PFS (95% CI)	HR	*P* value
Tivozanib	260	11.9 mos (9.3–14.7)	0.797	0.042
Sorafenib	257	9.1 mos (7.3–9.5)		

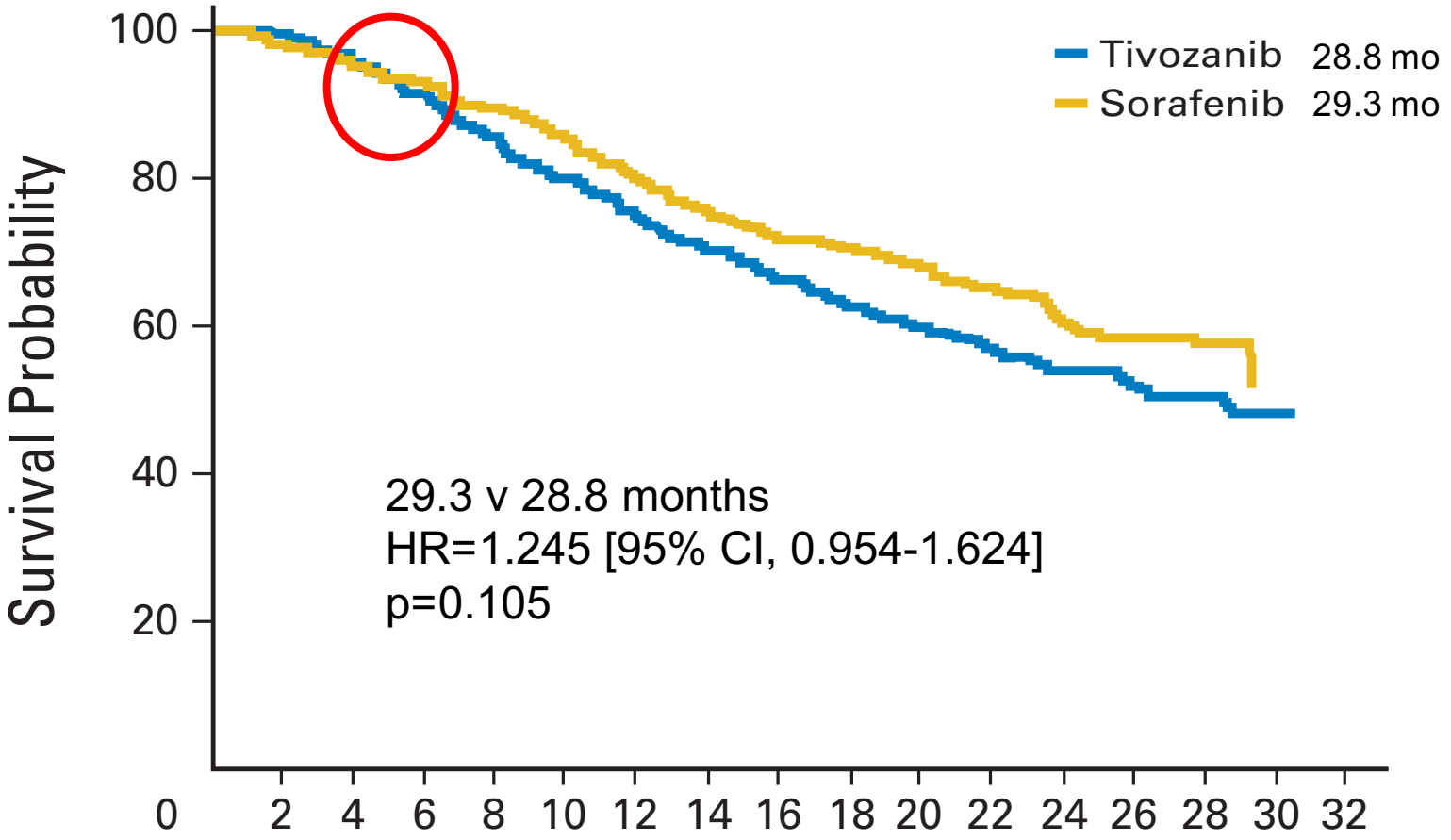


Progression-free survival: Treatment-naïve for metastatic RCC (independent review)

	N	Median PFS (95% CI)	HR	*P* value
Tivozanib	181	12.7 mos (9.1–15.0)	0.756	0.037
Sorafenib	181	9.1 mos (7.3–10.8)		



Aïe



No. at risk																	
Tivozanib	260	256	241	227	211	198	183	170	159	148	142	133	125	89	39	2	0
Sorafenib	257	249	241	232	218	208	194	181	170	167	157	151	137	98	43	3	0

Motzer et al. JCO 2013

Phase 3 positive = AMM ?

- Exemple de tivozanib
- Problématique du post étude
  - Ici cross over

1 vs 2 = ?

Category	Overall Population			
	Tivozanib (n = 260)		Sorafenib (n = 257)	
	No.	%	No.	%
Patients who discontinued assigned therapy*	190	73†	226	88
Patients with next-line therapy	68	26	168	65
Patients with next-line targeted therapy	34	13	162	63
VEGFR inhibitor	18	7	158	61
Tivozanib	0		156	61
mTOR inhibitor	16	6	4	2
Cytokines	14	5	3	1
Radiotherapy	10	4	2	1
Other	10	4	1	< 1

Motzer et al. JCO 2013

Séquentiel

517 pts

R
A
N

2 lignes T. Ciblées > 1 ligne ?

Motzer et al. JCO 2013

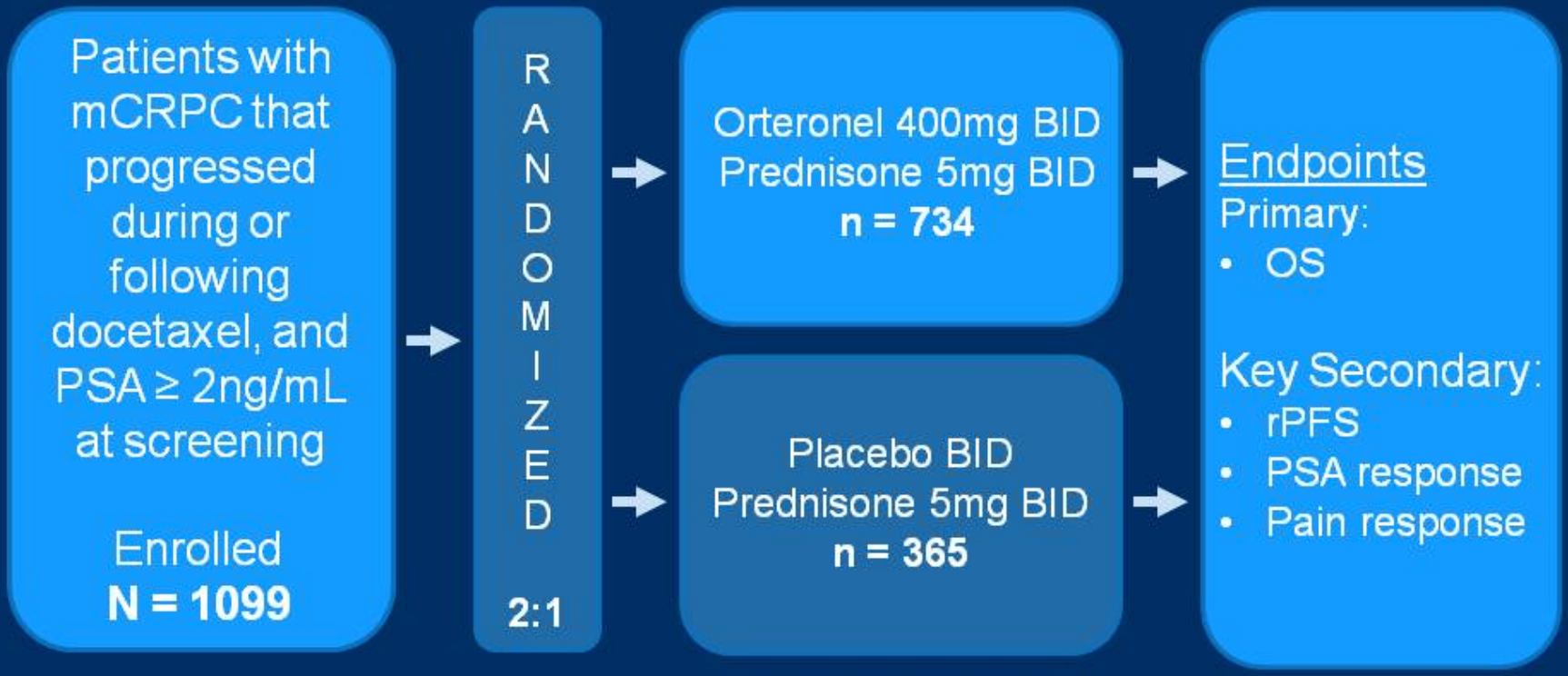
Results from a phase 3, randomized, double-blind, multicenter, placebo-controlled trial of orteronel (TAK-700) plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) that has progressed during or following docetaxel-based therapy (ELM-PC 5 trial)

Robert Dreicer,[1] Robert Jones,[2] Stéphane Oudard,[3] Eleni Efstathiou,[4] Fred Saad,[5] Ronald de Wit,[6] Johann De Bono,[7] Connie Lee,[8] Bindu Tejura,[8] David Agus,[9] Niels Borgstein,[8] Joaquim Bellmunt,[9] Karim Fizazi[10]

Presented at the **Genitourinary Cancers Symposium**

[1]Cleveland Clinic, Cleveland, OH, USA; [2]Institute of Cancer Sciences, University of Glasgow, Glasgow, UK; [3]Université Paris Descartes, Paris, France; [4]University of Athens Medical School, Athens, Greece; [5]University of Montreal Hospital Center, Montreal, QC, Canada; [6]Erasmus University Medical Center, Rotterdam, The Netherlands; [7]The Institute of Cancer Research, London, UK; [8]Takeda Pharmaceuticals International Co., Cambridge, MA, USA; [9]University of Southern California, Los Angeles, CA, USA; [9]Dana-Farber and Brigham and Women's Cancer Center, Boston, MA, USA; [10]Institut Gustave Roussy, University of Paris Sud, Villejuif, France

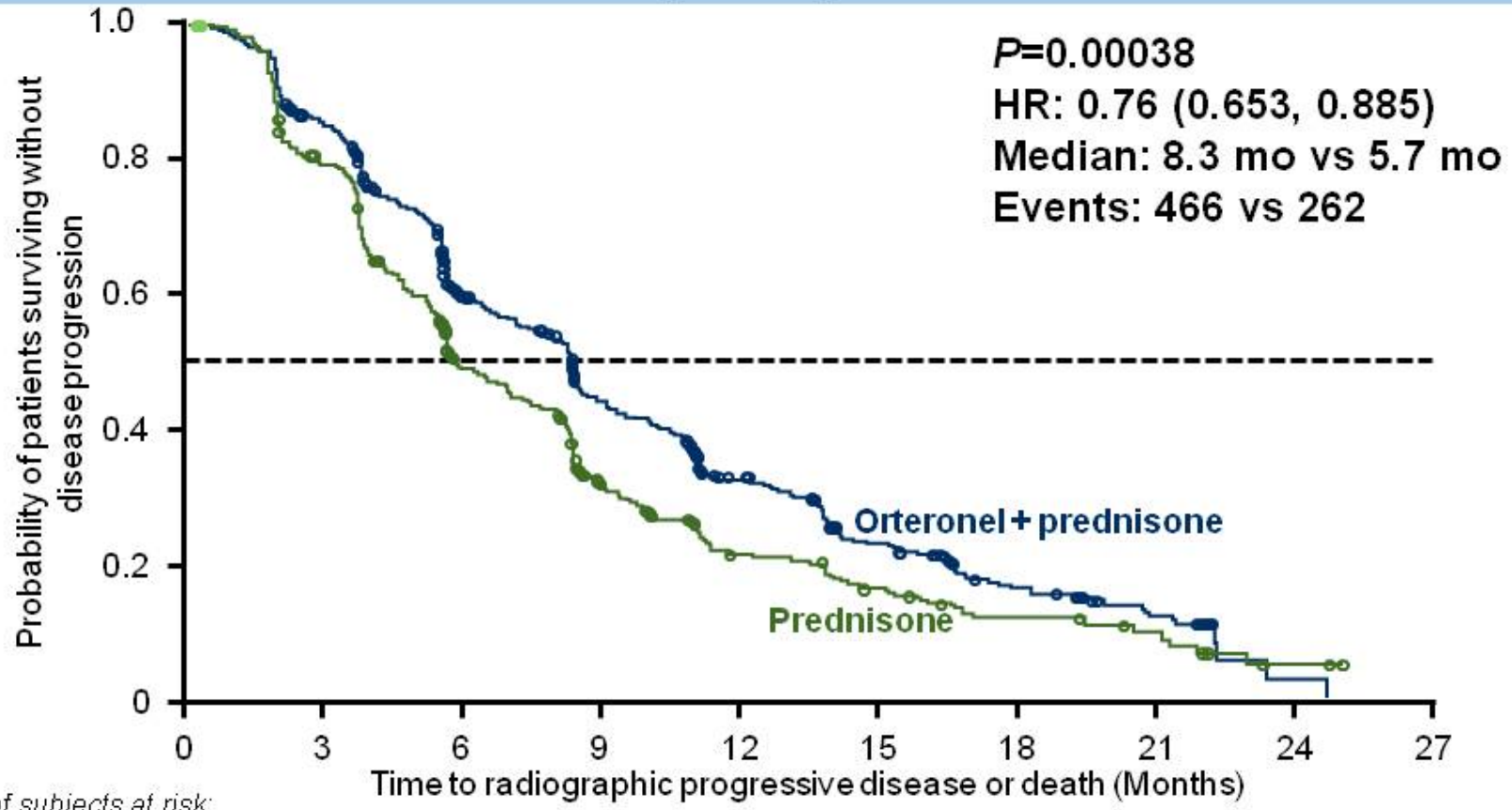
ELM-PC 5 Study Design



Presented at the **Genitourinary Cancers Symposium**

Presented By Robert Dreicer, MD at 2014 Genitourinary Cancers Symposium

Radiographic Progression-Free Survival benefit observed with orteronel plus prednisone



# of subjects at risk:

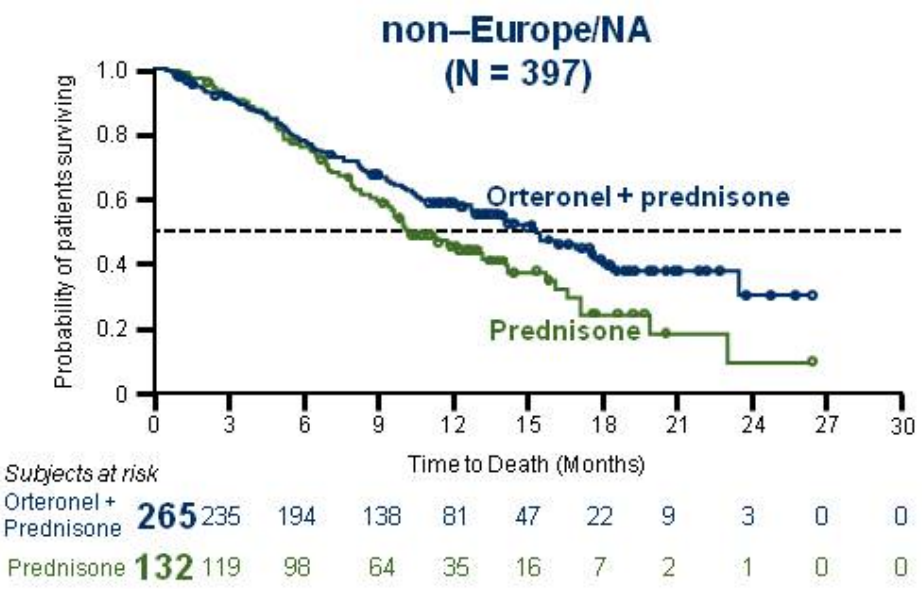
Orteronel + Prednisone	**734**	553	334	212	130	78	39	17	1	0
Prednisone	**365**	264	138	75	44	29	16	9	2	0

112 (15%) and 74 (20%) patients in the orteronel plus prednisone and prednisone groups, respectively, discontinued before radiographic progression.

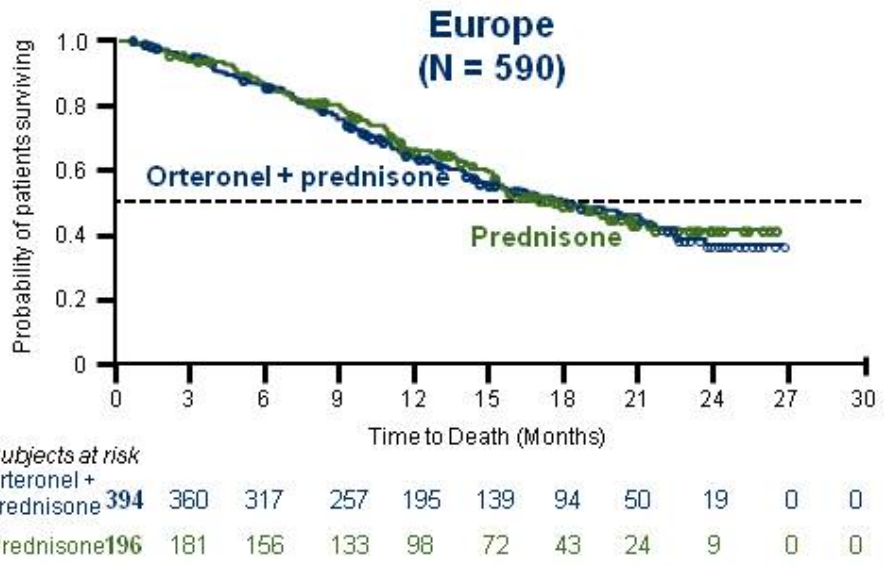
Presented at the **Genitourinary Cancers Symposium**

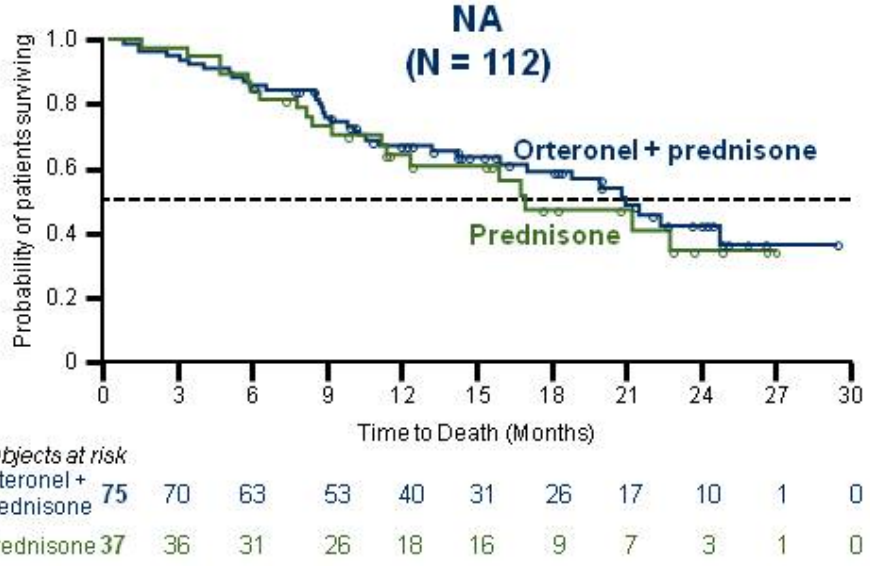
Presented By Robert Dreicer, MD at 2014 Genitourinary Cancers Symposium

Regional analysis of OS

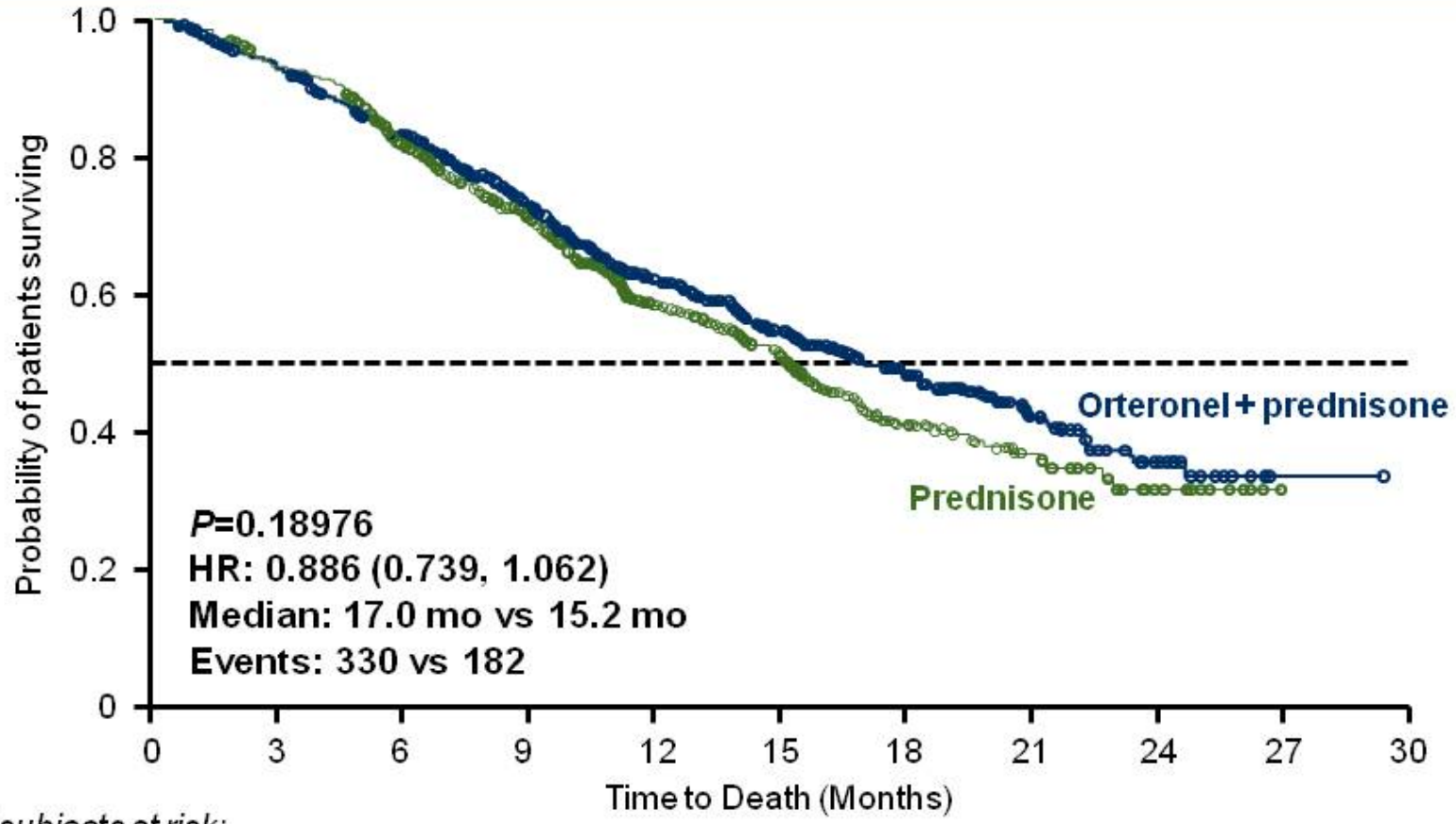


OS	non-Europe/NA		Europe		NA	
Log-rank *P*-value	**0.019**		0.721		0.680	
HR	**0.709** (0.531, 0.946)		1.048 (0.810, 1.356)		0.889 (0.508, 1.557)	
Median (mo)	**15.3**	**10.1**	18.3	17.8	20.9	16.9





Primary Endpoint: Overall Survival



# of subjects at risk:

Orteronel + Prednisone	**734**	665	574	448	316	217	142	76	32	1	0
Prednisone	**365**	336	285	223	151	104	59	33	13	1	0

Median follow-up time: 10.7 months (range, 0.2–29.5)

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Subsequent therapies

- A smaller percentage of patients received subsequent therapy in the non-Europe/NA population; possibly due to limited access to abiraterone and no access to enzalutamide

	Europe N = 586	non-Europe/NA N = 397	NA N = 112
Patients with ≥ 1 subsequent therapy, %	53	38	54
abiraterone	28	**8**	26
cabazitaxel	18	11	20
dexamethasone	9	18	11
docetaxel	7	6	5
enzalutamide	6	**0**	12

Presented By Robert Dreicer, MD at 2014 Genitourinary Cancers Symposium

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Grille de Lecture

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- Randomisées
- Méthodes statistiques
- Recueil données / Endpoint