Highlights ESMO 2024 urologie

10/10/2024

Nouvelle-Aquitaine

Diego Teyssonneau

Liens d’intérêts

Novartis, BMS, EISAI, Ipsen, Janssen, Pfizer, Astellas, Astrazeneca, Sandoz, Viatris

NIAGARA

ORIGINAL ARTICLE

Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer

T. Powles, J.W.F. Catto, M.D. Galsky, H. Al-Ahmadie, J.J. Meeks, H. Nishiyama, T.Q. Vu, L. Antonuzzo, P. Wiechno, V. Atduev, A.G. Kann, T.-H. Kim, C. Suárez, C.-H. Chang, F. Roghmann, M. Özgüroğlu, B.J. Eigl, N. Oliveira, T. Buchler, M. Gadot, Y. Zakharia, J. Armstrong, A. Gupta, S. Hois, and M.S. van der Heijden, for the NIAGARA Investigators*

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Contexte

- Environ 50% de rechute après chimiothérapie néoadjuvante puis cystectomie
- CheckMate 274 et AMBASSADOR positives en adjuvant, sur une population sélectionnée
- Intérêt d'évaluer un traitement péri-opératoire avec tumeur en place

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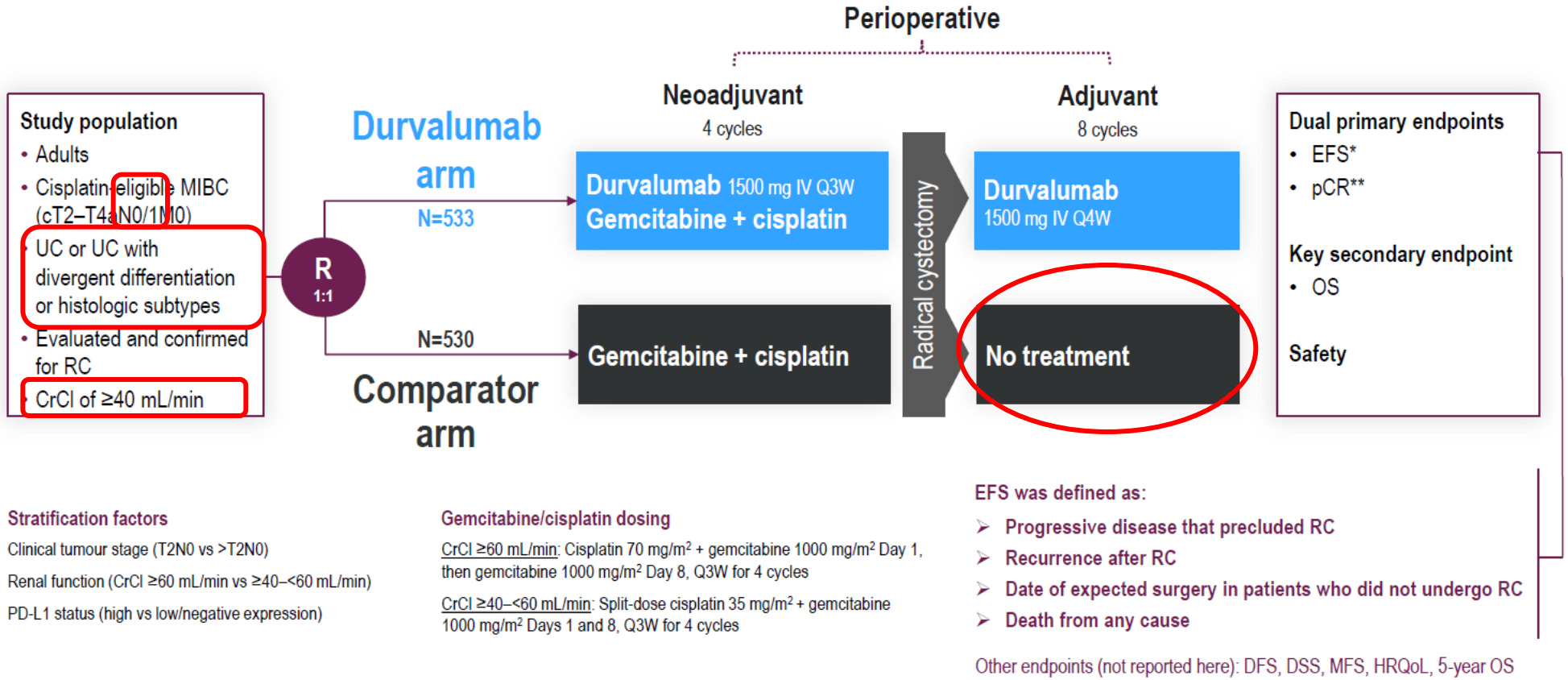
Design

NIAGARA: Study Design



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Population

Characteristics		Durvalumab arm N=533	Comparator arm N=530
Age	Median, years (range)	65 (34–84)	66 (32–83)
Sex, %	Male	82	82
Race, %	White	66	68
	Asian	29	27
	Black/Other	2	1
	Not reported	3	4
ECOG PS, %	0	78	78
	1	22	22
Smoker, %	Yes (current or former)	71	75
Renal function*, %	CrCl ≥60 mL/min	81	81
	CrCl ≥40–<60 mL/min	19	19
Tumour stage*, %	T2N0	40	40
	>T2N0	60	60
PD-L1 expression†, %	High	73	73
	Low/negative	27	27
Histology, %	UC	86	83
	UC with divergent differentiation or histologic subtypes	14	17
Regional lymph nodes, %	N0	95	94
	N1	5	6

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EFS

NIAGARA: Event-free Survival by Blinded Independent Central Review (ITT)

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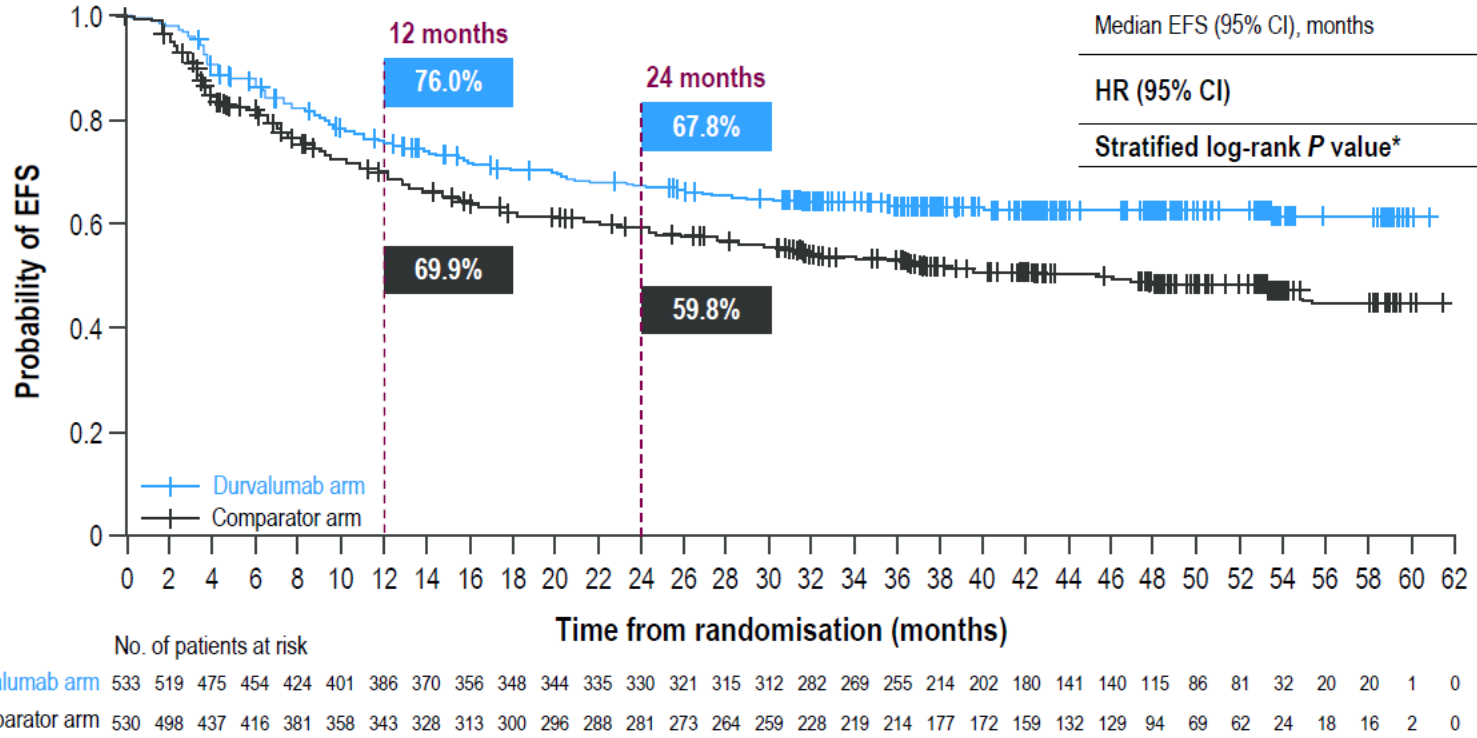
	Durvalumab arm N=533	Comparator arm N=530
Number of events, n (%)	187 (35.1)	246 (46.4)
Median EFS (95% CI), months	NR (NR–NR)	46.1 (32.2–NR)
HR (95% CI)	**0.68 (0.56–0.82)**	
Stratified log-rank *P* value*	**<0.0001**	



Median follow-up in censored patients: 42.3 months (range, 0.03–61.3)

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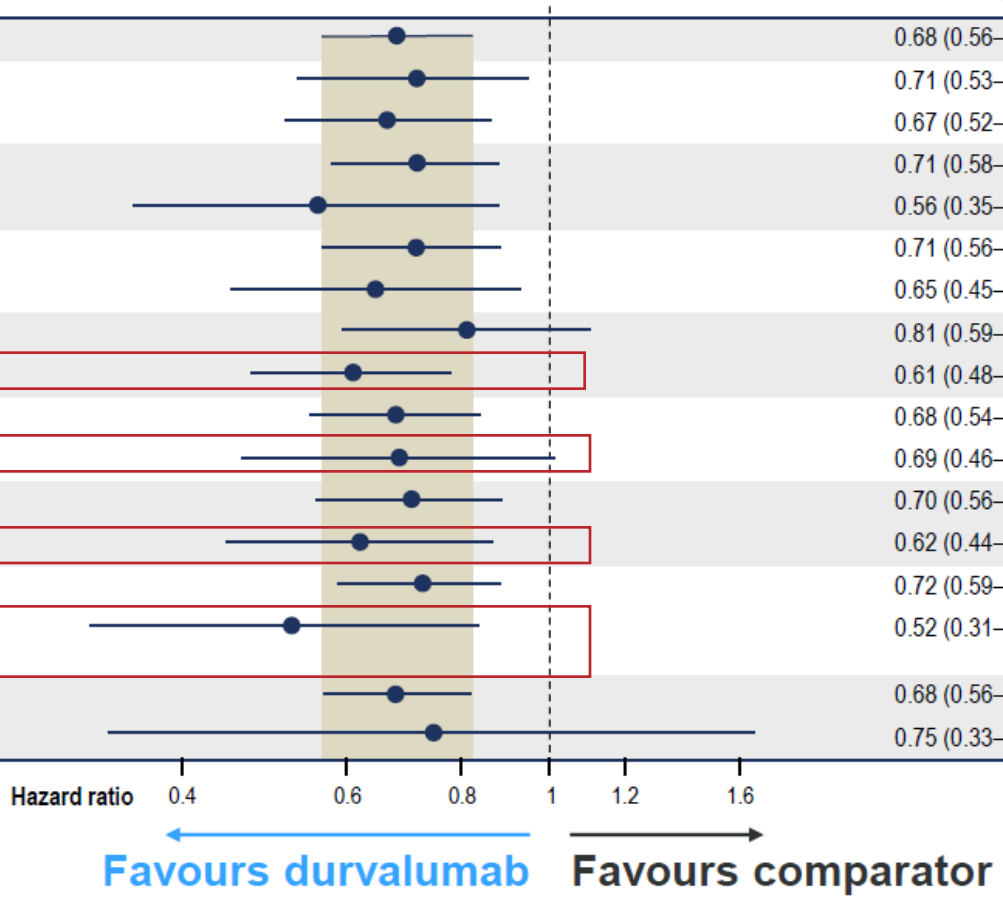
EFS : sous-groupes

Subgroup	Category	N	Hazard ratio (95% CI)
All patients		1063	0.68 (0.56–0.82)
Age at randomisation	<65 years	499	0.71 (0.53–0.94)
	≥65 years	564	0.67 (0.52–0.86)
Sex	Male	870	0.71 (0.58–0.88)
	Female	193	0.56 (0.35–0.88)
Race	White	712	0.71 (0.56–0.89)
	Non-White	315	0.65 (0.45–0.92)
Tumour stage at baseline	T2N0	428	0.81 (0.59–1.10)
	>T2N0	635	0.61 (0.48–0.78)
Renal function at baseline	CrCl ≥60 mL/min	862	0.68 (0.54–0.84)
	CrCl ≥40–<60 mL/min	201	0.69 (0.46–1.01)
PD-L1 expression at baseline*	High	777	0.70 (0.56–0.88)
	Low/negative	286	0.62 (0.44–0.87)
Histology at baseline	UC	898	0.72 (0.59–0.89)
	UC with divergent differentiation or histologic subtypes	165	0.52 (0.31–0.84)
Lymph node positive at baseline	N0	1005	0.68 (0.56–0.83)
	N1	58	0.75 (0.33–1.64)



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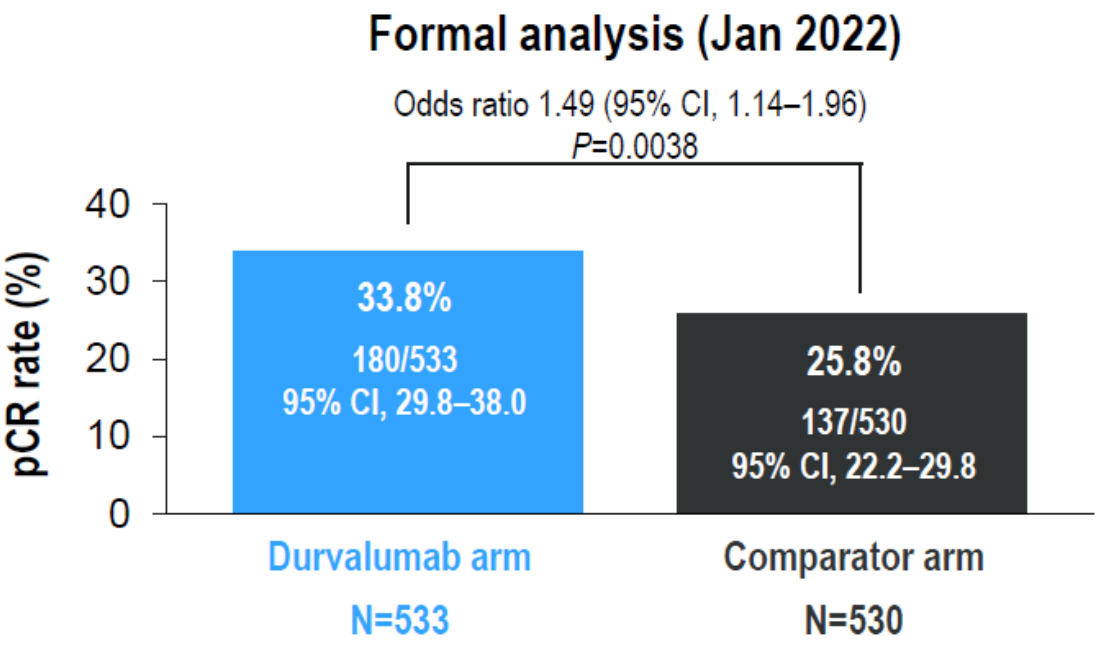
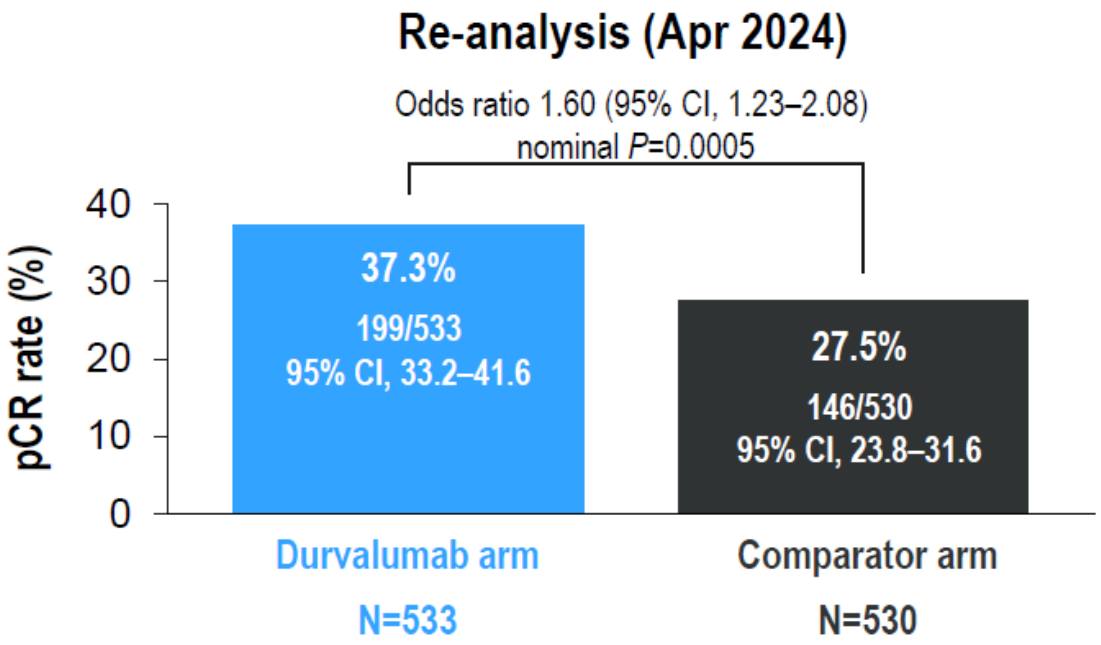
pCR





- The planned formal analysis for pCR was not statistically significant (threshold for significance, p-value 0.001)
- 59 evaluable samples were incorrectly considered non-responders rather than their true result*

- The re-analysis showed nominal statistical significance in favour of the durvalumab arm
- This analysis includes the results of the 59 omitted samples (28 additional pCRs)*

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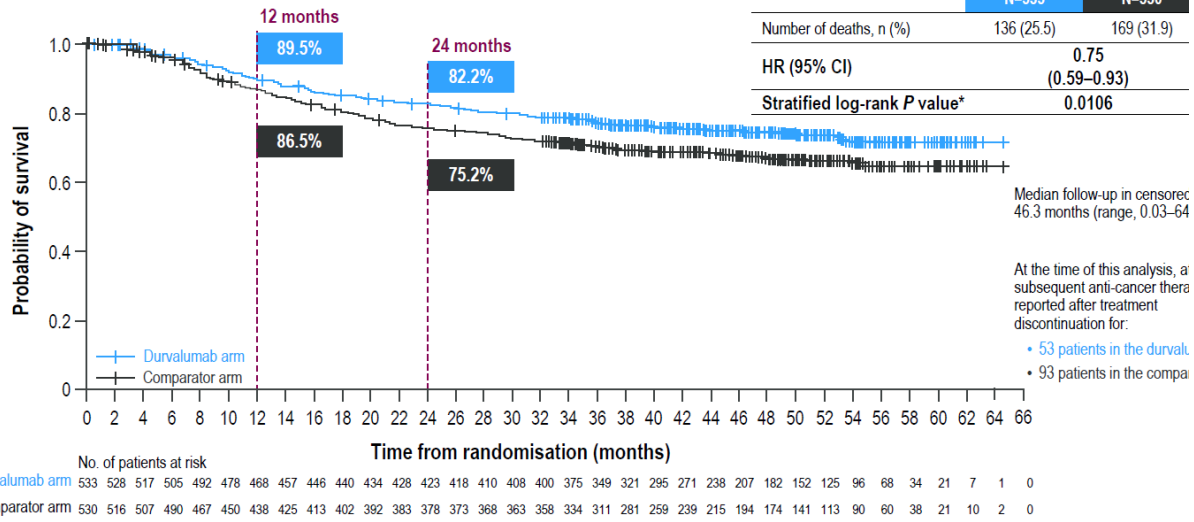
OS

NIAGARA: Overall Survival (ITT)

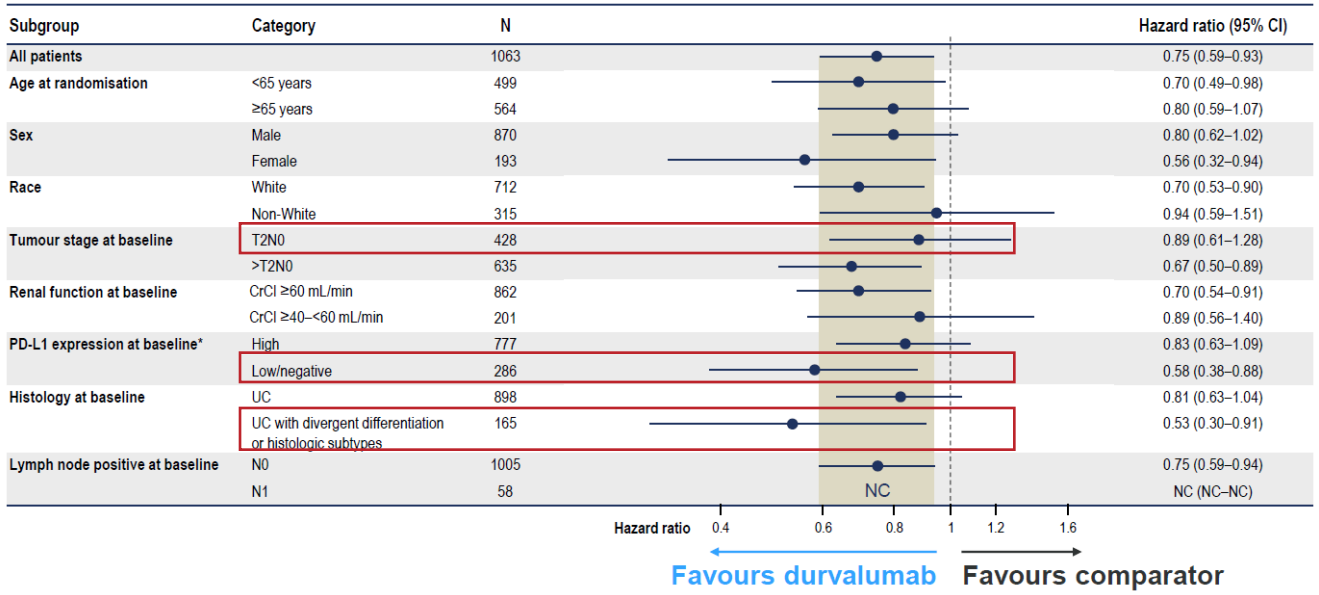


	Durvalumab arm N=533	Comparator arm N=530
Number of deaths, n (%)	136 (25.5)	169 (31.9)
HR (95% CI)	0.75 (0.59–0.93)	
Stratified log-rank *P* value*	0.0106	

Median follow-up in censored 46.3 months (range, 0.03–64

At the time of this analysis, a subsequent anti-cancer thera reported after treatment discontinuation for:

- 53 patients in the durvalu
- 93 patients in the compa



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Toxicité

Overall study period (unless otherwise stated)	Durvalumab arm N=530	Comparator arm N=526
AEs of any cause, n (%)	527 (99)	525 (100)
Grade 3 or 4	368 (69)	355 (68)
Serious AEs	326 (62)	287 (55)
Outcome of death	27 (5)	29 (6)
Leading to discontinuation of study treatment	112 (21)	80 (15)
Leading to discontinuation of neoadjuvant durvalumab	50 (9)	---
Leading to discontinuation of NAC	72 (14)	80 (15)
Leading to patient not undergoing RC	6 (1)	7 (1)
Leading to delay in surgery*	9 (2)	6 (1)
Leading to discontinuation of adjuvant durvalumab	30/383† (8)	---
AEs possibly related to any treatment, n (%)‡	502 (95)	487 (93)
Grade 3 or 4 (treatment related)	215 (41)	215 (41)
Outcome of death (treatment related)	3 (0.6)	3 (0.6)
Any-grade immune-mediated AEs	111 (21)	16 (3)

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Conclusion

- 1er essai de phase 3 évaluant l'impact des ICI en péri-opératoire
- Positif en EFS et OS pour la plupart des sous-groupes
- Toxicité acceptable, pas de retard de chirurgie

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Discussion

- Population large
- Cddp fractionné autorisé
- Bonne tolérance
- Résultats impactants

- Pas ddMVAC (VESPER)
  - pCR inférieure
  - GC<ddMVAC en OS
- Quelle part de du néo vs adjuvant ?

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Discussion

- Population large
- Cddp fractionné autorisé
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Pas ddMVAC (VESPER)
- pCR inférieure
- GC<ddMVAC en OS

Quelle part de du néo vs adjuvant ? →
- Suivi de données selon le ypT
- ctDNA

Vers un nouveau standard ?

TiNivo-2

Tivozanib plus nivolumab versus tivozanib monotherapy in patients with renal cell carcinoma following an immune checkpoint inhibitor: results of the phase 3 TiNivo-2 Study

Toni K Choueiri, Laurence Albiges, Philippe Barthélémy, Roberto Iacovelli, Sheik Emambux, Javier Molina-Cerrillo, Benjamin Garmezy, Pedro Barata, Arnab Basu, Maria T Bourlon, Helen Moon, Raffaele Ratta, Rana R McKay, Alexander Chehrazi-Raffle, Hans Hammers, Daniel Y C Heng, Edgar Braendle, Kathryn E Beckermann, Bradley A McGregor, Robert J Motzer**

TiNivo-2

CONTEXTE

- L1 ccRCC : doublet comprenant un ICI
- Lignes suivantes ne comprenant que des anti-VEGF ou mTOR
- Intérêt du rechallenge d'ICI en suspens
  - CONTACT-03 négative

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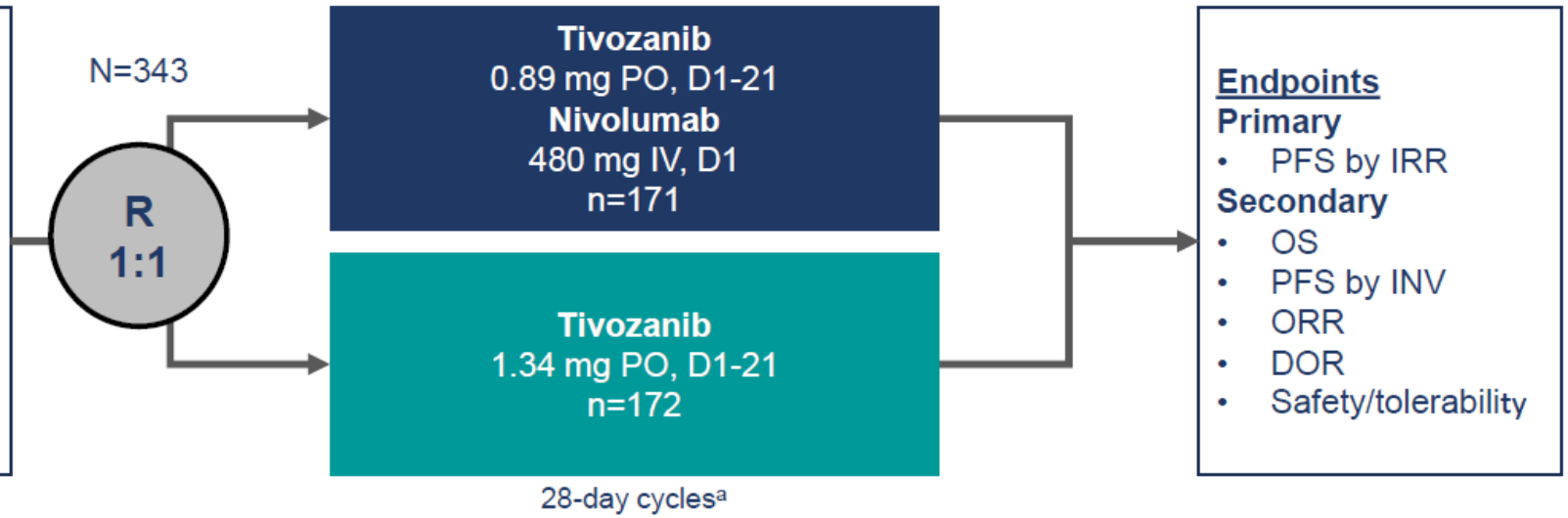
TiNivo-2

DESIGN

Locally advanced or metastatic clear cell RCC after progression on 1 or 2 lines of therapy, one of which was an ICI:

- Progression during or following ≥6 weeks of treatment with an ICI
- Time from immediate prior line of therapy to randomization ≤6 months
- Measurable disease (RECIST v1.1)
- ECOG PS: 0 or 1



Stratification Factors

- IMDC risk category
- Prior therapy (ICI as most recent therapy or not)

Statistical Analysis

- 220 PFS events, statistically powered to detected an improvement of 4 months in PFS (HR=0.67)
- Stratified log-rank test with a two-sided 5% significance level

Key Considerations

- Reduced dose of tivozanib in combination arm was agreed with regulatory authorities due to potential risk of higher rate of grade 3/4 hypertension
- Prior therapy (ICI as most recent therapy or not)
  - Test if ICI break impacts outcome (to resensitize the immune system to ICI therapy)

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TiNivo-2

POPULATION

Characteristic	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
Age, years		
Median (range)	64 (37-87)	63 (33-82)
Sex, n (%)		
Female	46 (27)	38 (22)
Male	125 (73)	134 (78)
Race, n (%)		
White	112 (65)	107 (62)
Asian	1 (<1)	0
Black or African American	2 (1)	8 (5)
Not reported	56 (33)	57 (33)
ECOG PS, n (%)		
0	76 (44)	85 (49)
1	94 (55)	87 (51)
Missing	1 (<1)	0

Characteristic	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
IMDC risk category, n (%)		
Favorable	30 (18)	31 (18)
Intermediate	114 (67)	113 (66)
Poor	27 (16)	28 (16)
Prior lines of therapy, n (%)		
1	111 (65)	105 (61)
2	60 (35)	67 (39)
Most recent therapy, n (%)		
ICI	122 (71)	122 (71)
Non-ICI	49 (29)	50 (29)
Prior VEGFR-TKI use, n (%)		
0	53 (31)	53 (31)
1	96 (56)	101 (58)
2	22 (13)	18 (11)

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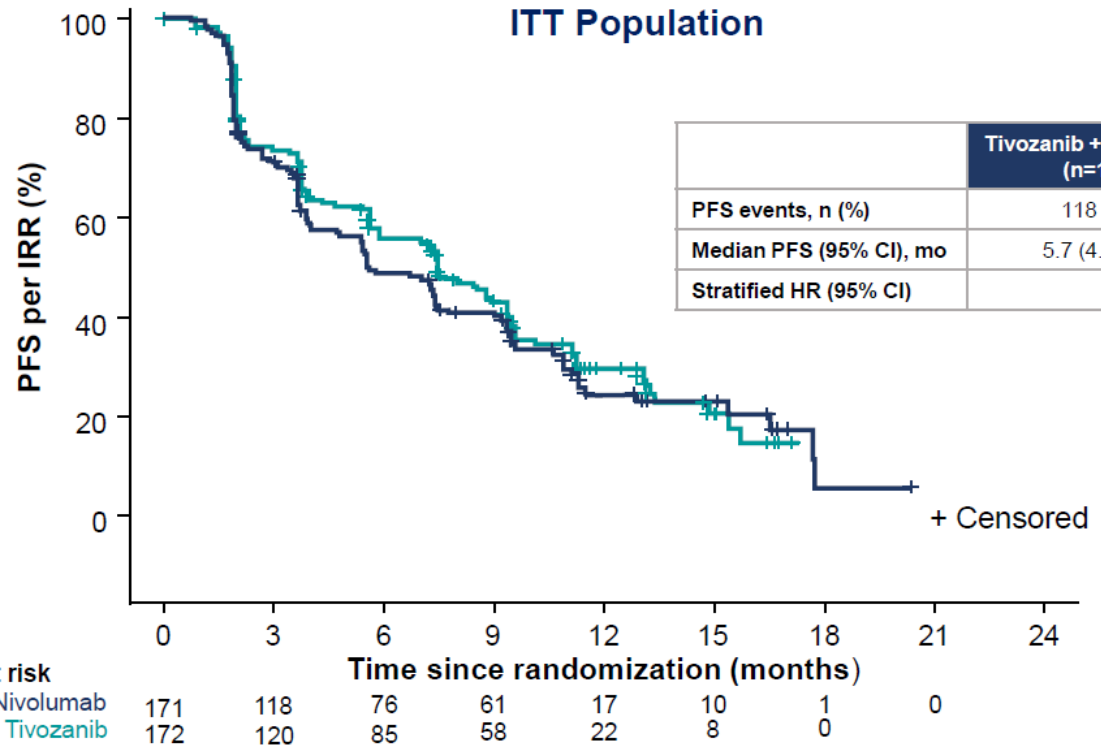
RESULTATS

Primary Analysis of Centrally Reviewed PFS (primary endpoint)



	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
PFS events, n (%)	118 (69)	112 (65)
Median PFS (95% CI), mo	5.7 (4.0-7.4)	7.4 (5.6-9.2)
Stratified HR (95% CI)	1.10 (0.84-1.43); p=0.49	

Median follow-up was 11.8 months in the tivozanib + nivolumab cohort and 12.5 months in the tivozanib monotherapy arm

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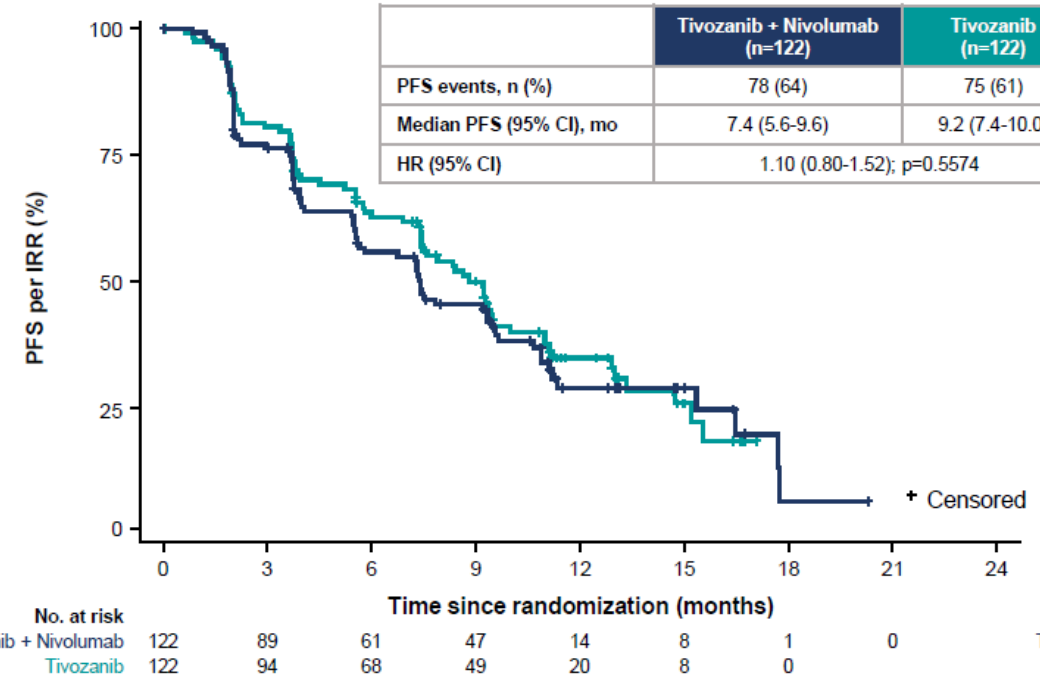
RESULTATS

Centrally Reviewed PFS by Most Recent Line of Therapy

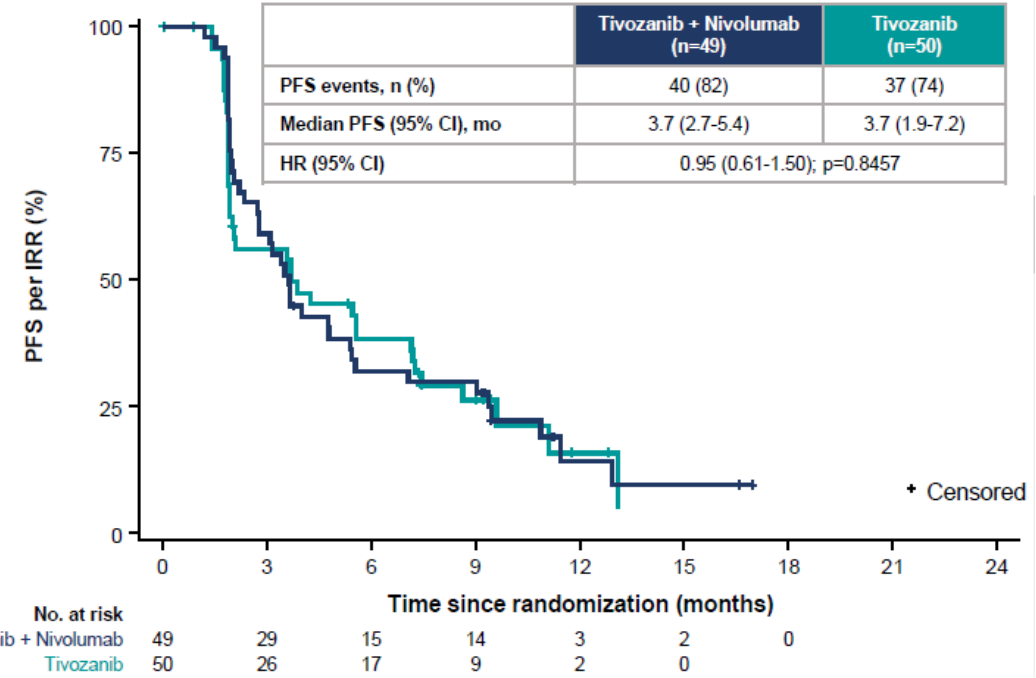
ICI as Most Recent Therapy

	Tivozanib + Nivolumab (n=122)	Tivozanib (n=122)
PFS events, n (%)	78 (64)	75 (61)
Median PFS (95% CI), mo	7.4 (5.6-9.6)	9.2 (7.4-10.0)
HR (95% CI)	1.10 (0.80-1.52); p=0.5574	



Non-ICI as Most Recent Therapy

	Tivozanib + Nivolumab (n=49)	Tivozanib (n=50)
PFS events, n (%)	40 (82)	37 (74)
Median PFS (95% CI), mo	3.7 (2.7-5.4)	3.7 (1.9-7.2)
HR (95% CI)	0.95 (0.61-1.50); p=0.8457	



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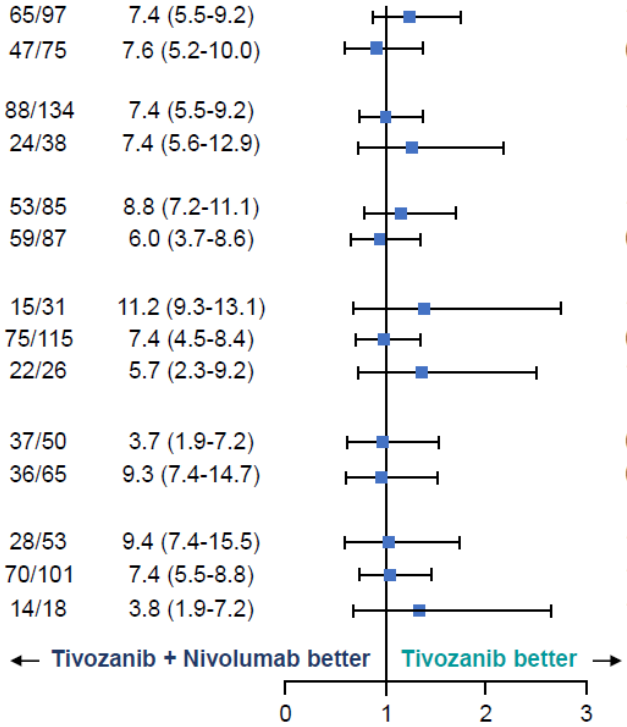
RESULTATS

Centrally Reviewed PFS by Subgroups

Category	Tivozanib + Nivolumab Event/N	Tivozanib + Nivolumab Median PFS (95% CI), months	Tivozanib Event/N	Tivozanib Median PFS (95% CI), months	PFS HR (95% CI)
Age					
<65 years	68/89	4.8 (3.7-7.3)	65/97	7.4 (5.5-9.2)	1.25 (0.89-1.76)
≥65 years	50/82	9.2 (5.5-9.6)	47/75	7.6 (5.2-10.0)	0.92 (0.61-1.37)
Sex					
Male	86/125	5.6 (3.9-7.5)	88/134	7.4 (5.5-9.2)	1.01 (0.75-1.36)
Female	32/46	6.7 (3.7-10.9)	24/38	7.4 (5.6-12.9)	1.27 (0.75-2.16)
ECOG PS					
0	52/76	7.3 (4.0-9.4)	53/85	8.8 (7.2-11.1)	1.15 (0.78-1.69)
1	66/94	5.5 (3.7-9.0)	59/87	6.0 (3.7-8.6)	0.95 (0.67-1.36)
IMDC risk category					
Favorable	18/30	9.3 (4.0-11.4)	15/31	11.2 (9.3-13.1)	1.37 (0.69-2.73)
Intermediate	78/114	5.7 (4.0-9.4)	75/115	7.4 (4.5-8.4)	0.99 (0.72-1.36)
Poor	22/27	3.7 (2.7-7.4)	22/26	5.7 (2.3-9.2)	1.35 (0.73-2.50)
VEGFR-TKI use in most recent line					
Yes	37/45	3.4 (2.2-4.8)	37/50	3.7 (1.9-7.2)	0.96 (0.61-1.52)
No	37/66	9.6 (7.5-11.2)	36/65	9.3 (7.4-14.7)	0.95 (0.60-1.51)
No. of previous VEGFR-TKIs (any prior line)					
0	29/53	9.6 (7.4-15.3)	28/53	9.4 (7.4-15.5)	1.03 (0.61-1.74)
1	69/96	5.4 (3.7-6.7)	70/101	7.4 (5.5-8.8)	1.04 (0.74-1.45)
2	20/22	3.1 (2.1-4.0)	14/18	3.8 (1.9-7.2)	1.33 (0.67-2.65)



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ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICI, immune checkpoint inhibitor; IMDC, International mRCC Database Consortium; IRR, independent radiology review; PFS, progression-free survival; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

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TiNivo-2

Conclusion

- 1er essai à évaluer le rechallenge d'un iPD-1
- Pas de bénéfice à l'ajout de NIVOLUMAB
- Confirme les résultats de CONTACT-03

SUNNIFORECAST

SUNNIFORECAST

CONTEXTE

- nccRCC : population très hétérogène
- Peu de traitements efficaces
- Impact majeur du doublet comprenant un ICI dans les ccRCC

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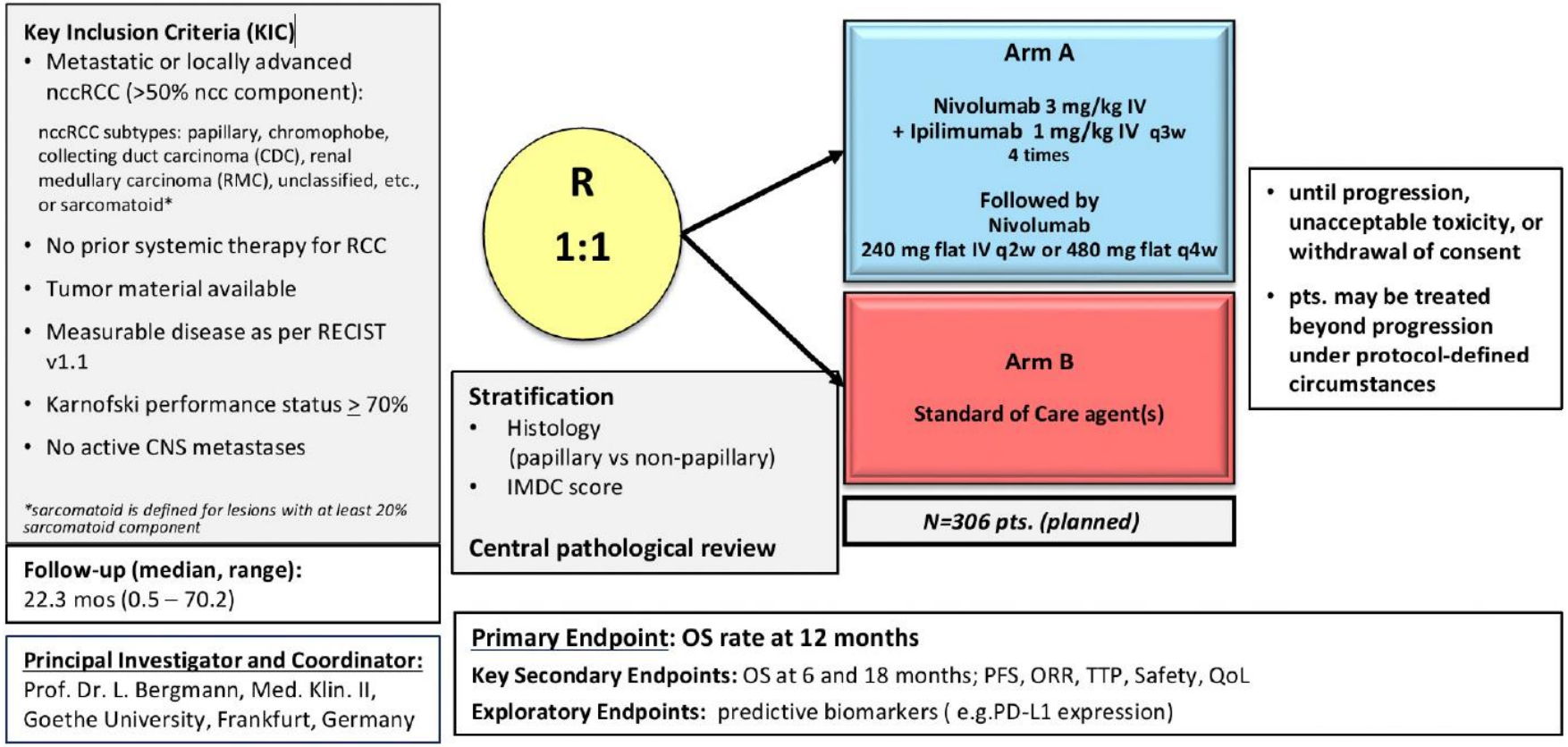
SUNNIFORECAST

DESIGN

SUNNIFORECAST – Study design



CNS, central nervous system; IV, intravenous; ORR, objective response rate; TTP time to progression; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PO, oral; PS, performance status; R, randomized; RCC, renal cell carcinoma.

Bergmann L et al. Oral presentation at ESMO 2024; September 13-17; Barcelona, Spain. Abstract LBA75

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POPULATION

Subtypes of nccRCC (central pathological review)	Total N=309	Ipilimumab/Nivolumab N=157	Standard of Care (SOC) N=152	*p-value*
Papillary RCC	178 (57.6 %)	89 (56.7%)	89 (58.6%)	
Chromophobe RCC	60 (19.4 %)	28 (17.8%)	32 (21.2%)	
MiT family translocation RCC	12 (3.9 %)	9 (5.7%)	3 (2.0%)	
Renal medullary carcinoma	3 (1.0 %)	0 (0.0%)	3 (2.0%)	
Translocation RCC (TFE, TEFEB)	5 (1.6%)	3 (1.9%)	2 (1.3%)	
Tubulocystic RCC	3 (1.0 %)	3 (1.9%)	0 (0.0%)	
Mucinous tubular and spindle cell carcinoma	1 (0.3 %)	1 (0.6%)	0 (0.0%)	*p=0.17*
Sarcomatoid	14 (4.5 %)	8 (5.1%)	6 (3.9%)	
Ductus Bellini carcinoma	3 (1.0%)	0 (0.0%)	3 (2.0%)	
Others	21 (6.7 %)	11 (7.0%)	10 (6.6%)	

***SOC**
- 124 x TKI
- 17 x TKI/IO
- 2x others

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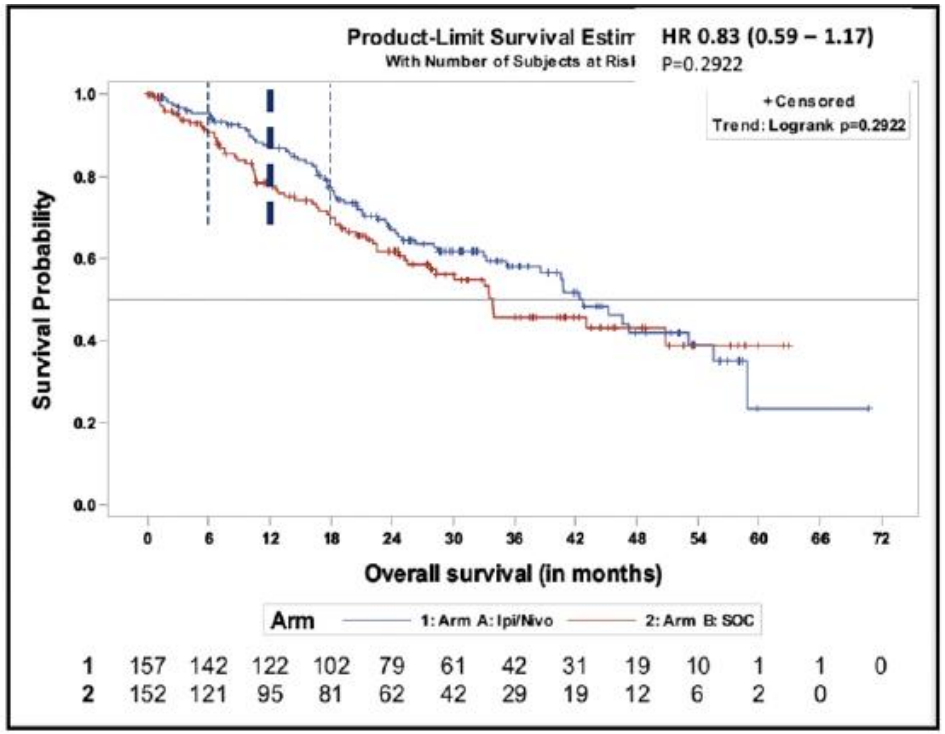
RESULTATS : OS

	Total N=309	Ipilimumab/ Nivolumab N=157	Standard of Care (SOC) N=152	*p-value*
OS rate at 12 mos (95%-CI)	**82.5%** (77.46% - 86.46%)	**86.9%** (80.24% - 91.46%)	**76.8%** (68.62% - 83.09%)	***p=0.0141***
OS rate at 6 mos (95%-CI)	92.8% (95.27% - 2.83%)	94.7% (89.72% - 97.32%)	90.0% (83.75% - 93.98%)	*p=0.067*
OS rate at 18 mos (95%-CI)	73.4% (67.67% - 78.28%)	76.6% (68.69% - 82.79%)	69.1% (60.25% - 76.34%)	*p=0.084*
OS mos (median, 95%-CI)	40.8 (33.2 - 47.21)	42.4 (35.24 – 55.54)	33.9 (25.52 – *)	*p=0.292*



Median follow-up: 24.3 mos (0.5 -70.2)

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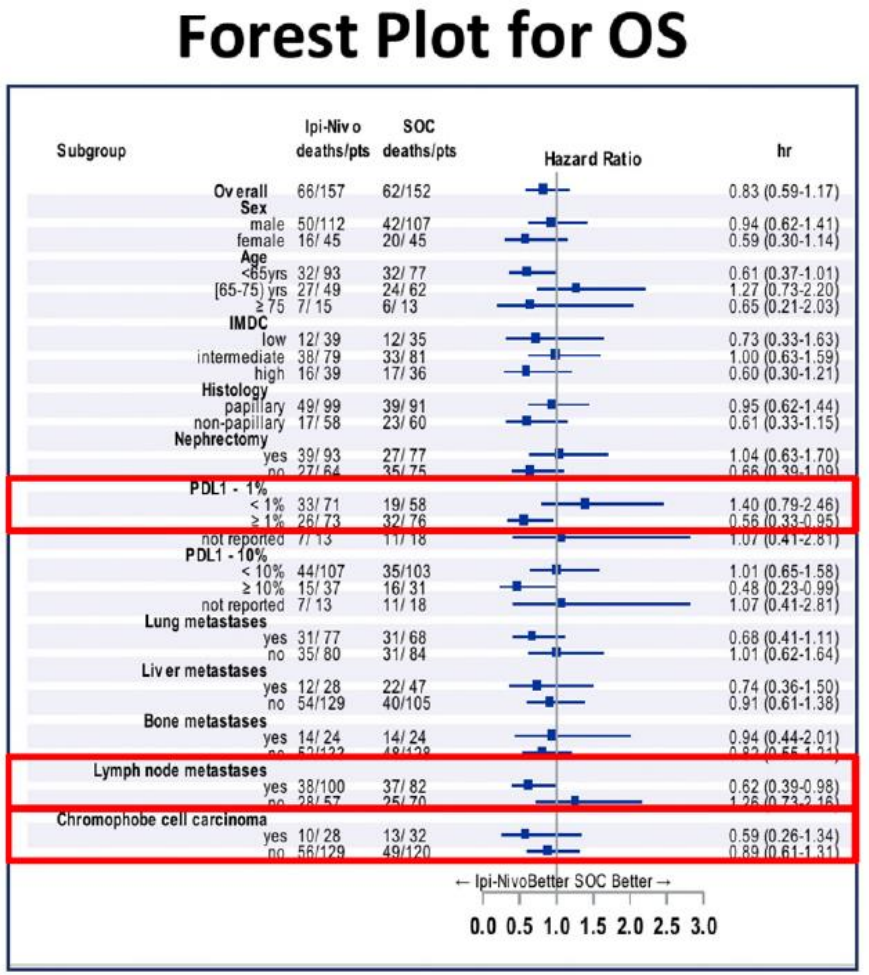
RESULTATS : sous groupes



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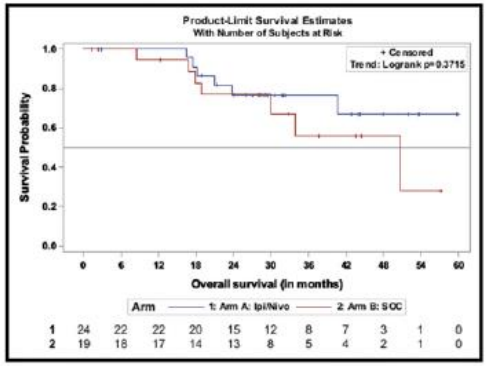
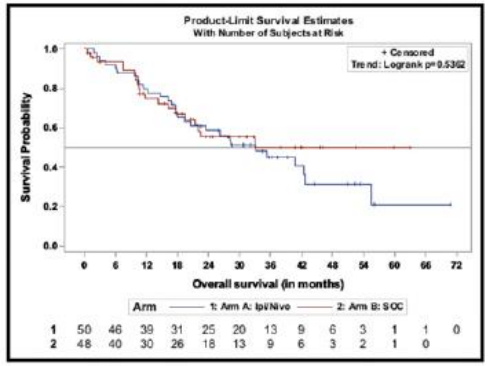
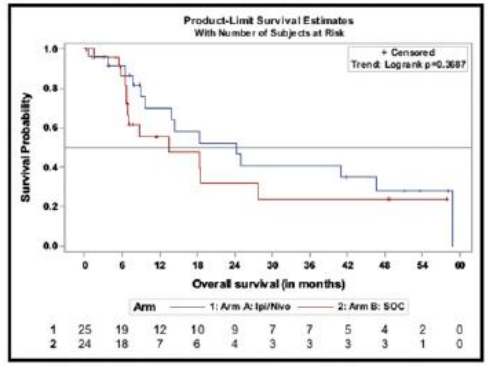
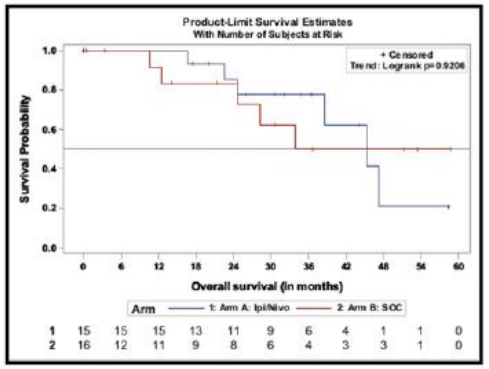
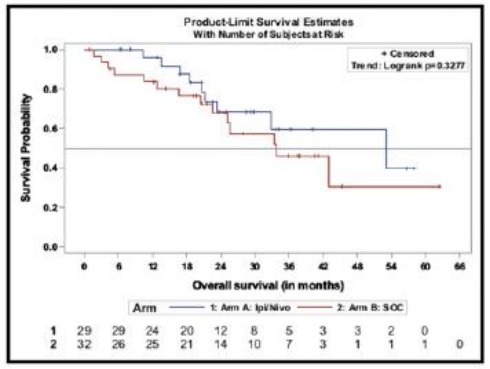
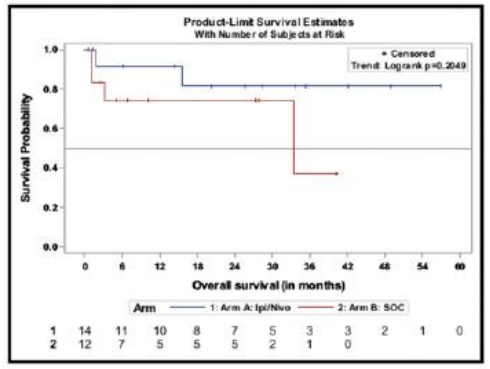
RESULTATS : papillaires

	favorable	intermediate	poor
Papillary RCC			
Non papillary RCC			

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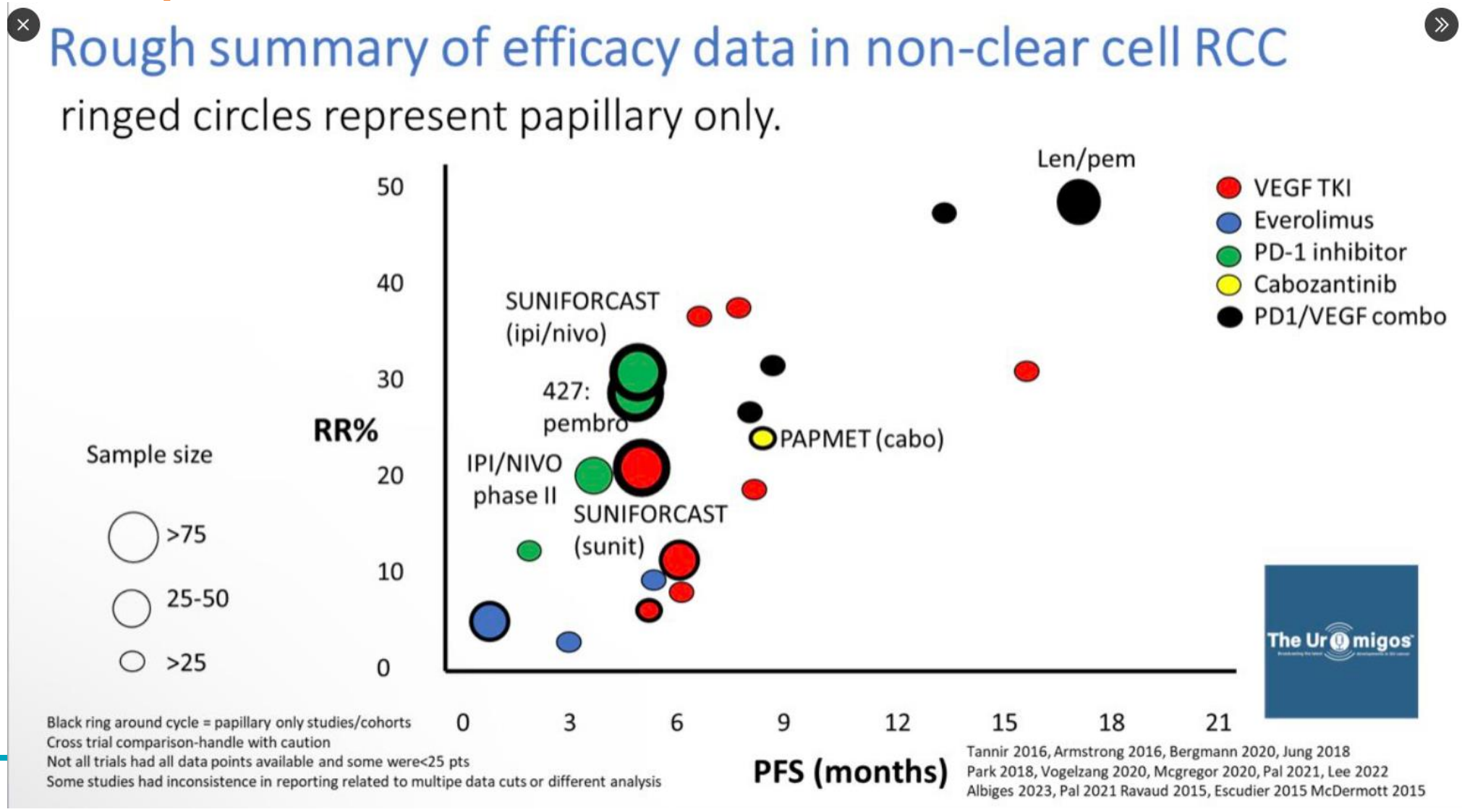
SUNNIFORECAST

Conclusion

- Positive sur son objectif primaire (OS à 12 mois) sur une population pauvre en traitement
- Profil de survie similaire entre papillaire et non papillaire
- Intérêt du statut PD-L1?
- Profil de tolérance intéressant

SUNNIFORECAST

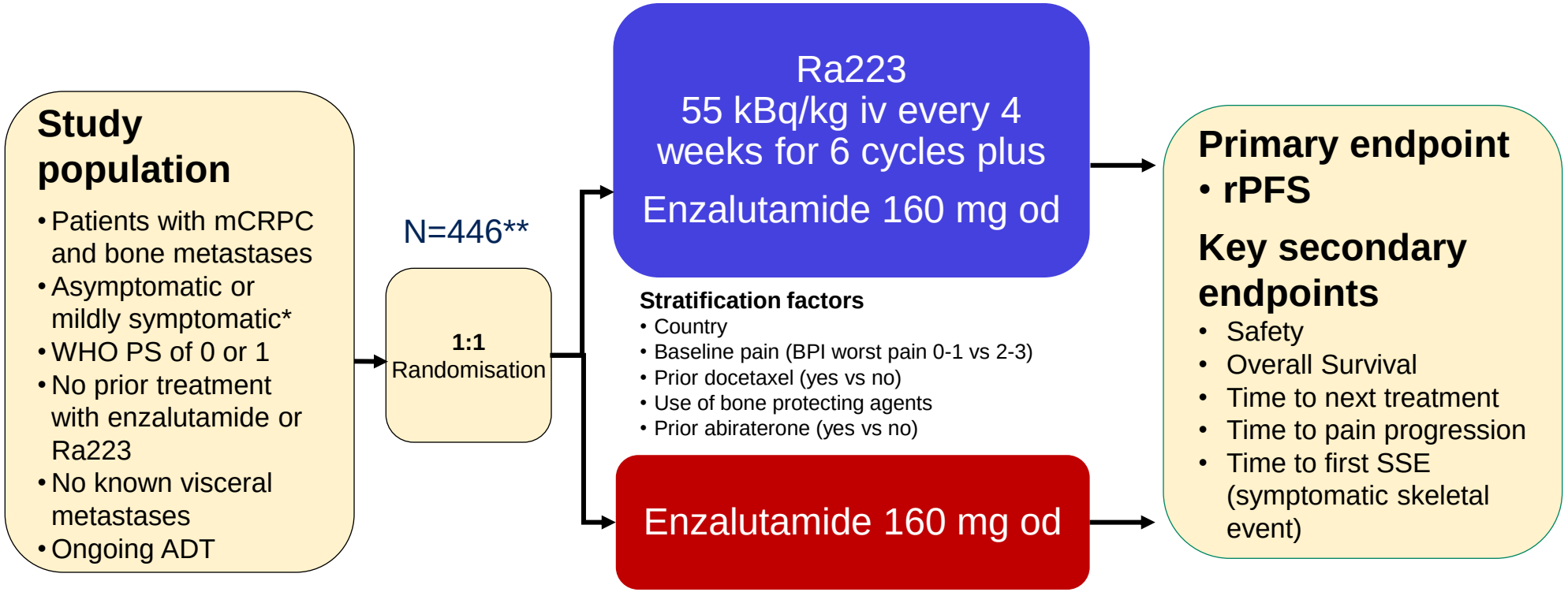
Perspectives



PEACE-3

PEACE-3

Design



*defined as brief pain inventory WP24 score < 4
** original target accrual N=560, adapted for slow accrual

Use of bone protecting agents (BPA) made mandatory (after inclusion of 119 patients)

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PEACE-3

Population

	Enza+Ra223 (N=222)	Enza (N=224)
	N (%)	N (%)
Age, Median (range) years	70.0 (43.0 - 90.0)	70.0 (47.0 - 90.0)
PSA, Median (Q25-Q75) ng/mL	25.3 (6.5 - 68.8)	23.0 (8.5 - 54.9)
WHO Performance status 0	152 (69)	154 (69)
Prior docetaxel(1)	67 (30.2)	66 (30)
Prior abiraterone(1)	4 (2)	7 (3)
Bone lesions(2)		
<10	109 (49)	105 (47)
≥10	93 (42)	99 (44)
Missing or diffuse lesions	20 (9)	20 (9)
Alkaline phosphatase		
≤ULN	127 (57)	107 (48)
>ULN	82 (37)	110 (49)
Missing	13 (6)	7 (3)
Extra-skeletal disease at baseline	77 (35)	73 (33)

(1) Prior docetaxel or abiraterone was allowed for mHSPC

(2) Per imaging guidelines, the type of bone lesions is reported by a radiologist and classified into focal, diffuse or equivocal. Only focal bone lesions can be counted.

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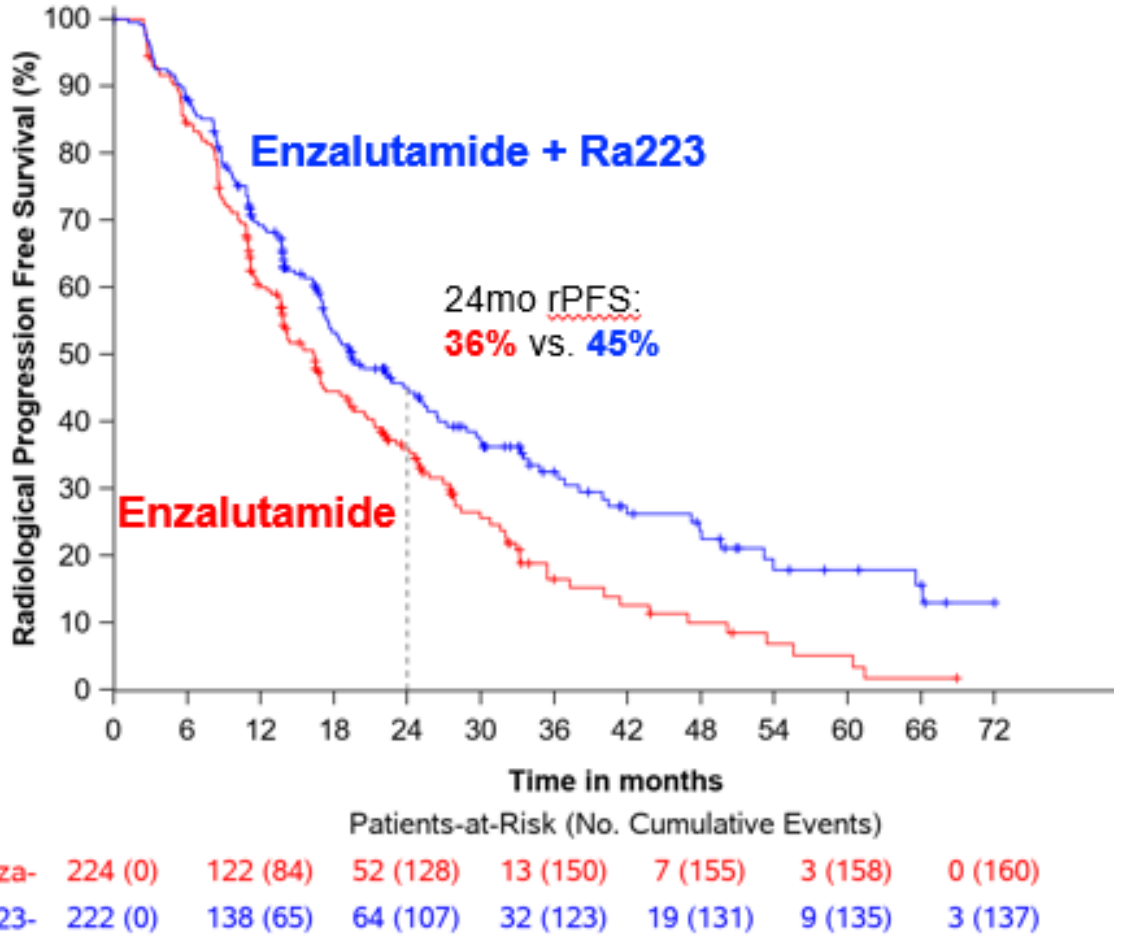
PEACE-3

PFS



Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	139/222	**19.4** (17.1-25.3) mo
Enzalutamide	160/224	**16.4** (13.8-19.2) mo
HR (95%CI)	**0.69** (0.54-0.87)	
Log-Rank p-value	**0.0009**	
Assumption of proportional hazard achieved		

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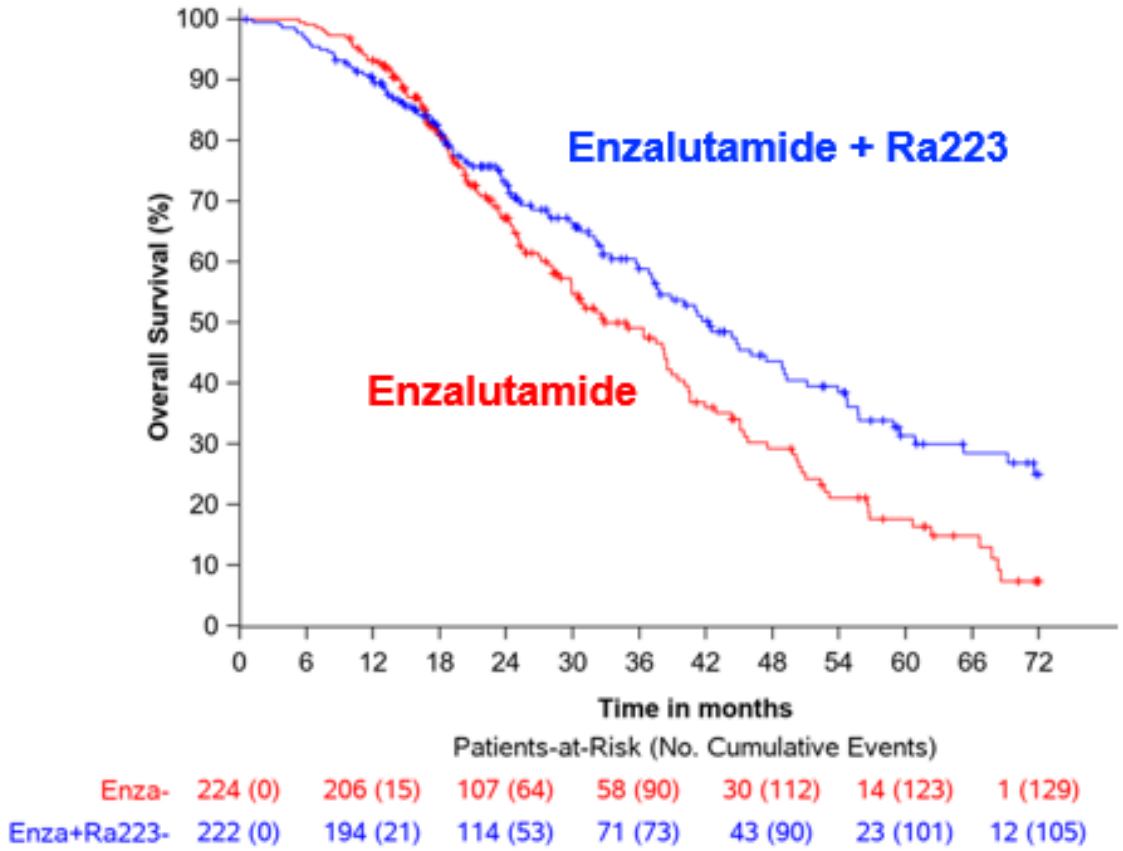
PEACE-3

OS



Arm	n/N	Median (95%CI)
Enzalutamide + Ra223	110/222	**42.3** (36.8-49.1) mo
Enzalutamide	129/224	**35.0** (28.8-38.9) mo
HR (95%CI)	**0.69** (0.52-0.90)	
Log-Rank p-value	**0.0031**	**<0.0034**

- Pre-set level of significance for interim analysis was ≤ 0.0034
- Due to non-proportional hazards plus lack of unequivocal significance for RMST (restricted mean survival time) sensitivity analysis, study will continue to final OS analysis

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PEACE-3

Toxicité

Patients	Enza+Ra223 (N=218) N (%)	Enza (N=224) N (%)
Adverse events (AEs)	218 (100)	216 (96)
Drug-related AEs	183 (84)	158 (71)
Serious AEs	93 (43)	66 (30)
Serious drug-related AEs	18 (8)	3 (1)
Grade 3-5 AEs	143 (66)	125 (56)
Grade 3-5 drug-related AEs	61 (28)	42 (19)
Death due to AE	7 (3)	4 (2)
Death due to a drug-related AE	0	0
Treatment discontinuation due to toxicity		
Enzalutamide	13 (8)	12 (7)
RA223	7 (3)	

Most common grade 3-5 treatment emergent AE (TEAE)	Enza+Ra223 (N=218) N (%)	Enza (N=224) N (%)
All		
Hypertension	73 (33.5)	77 (34.4)
Fatigue	12 (5.5)	4 (1.8)
Fracture	11 (5.1)	3 (1.3)
Anaemia	10 (4.6)	5 (2.2)
Neutropenia	10 (4.6)	0
Bone Pain	9 (4.1)	11 (4.9)
Weight Decreased	7 (3.2)	1 (0.4)
Spinal Cord Compression	6 (2.8)	8 (3.6)
Treatment related		
Hypertension	25 (11.5)	27 (12.1)
Fatigue	9 (4.1)	3 (1.3)
Anaemia	6 (2.8)	0
Neutropenia	7 (3.2)	0

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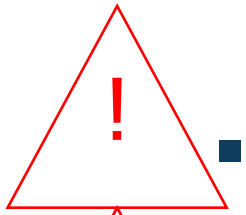
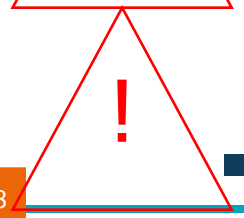
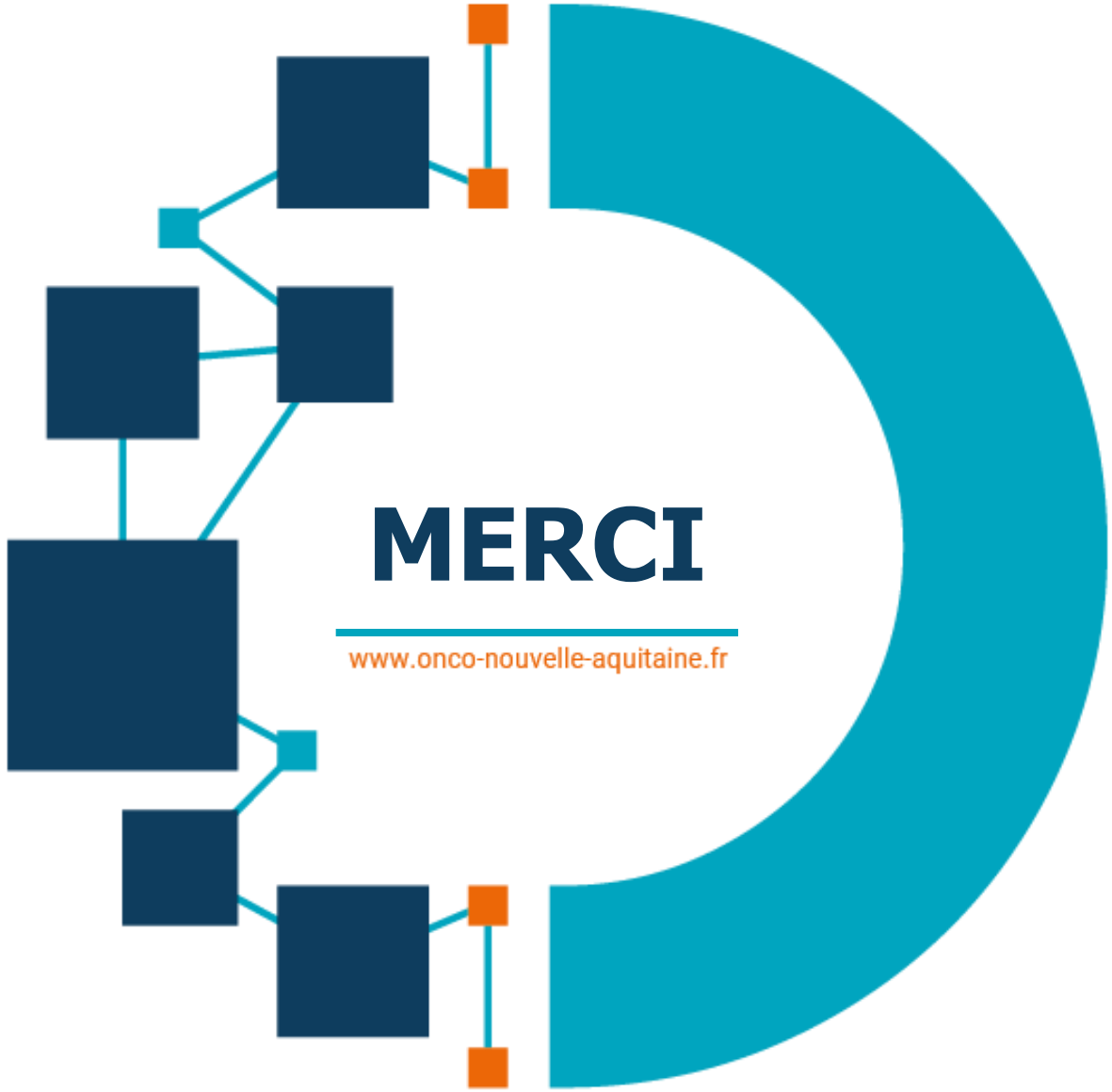
PEACE-3

Conclusion

- Replace à l'honneur le Ra223
- Effet synergique intéressant, peu toxique
- Quelle myélotoxicité pour la suite ?
- Agents anti-resorptif osseux
- Population non exposé aux NHT



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