Post ESMO 2023
Onco urologie

Courèche KADERBHAI
Oncologue médical
CGFL - Dijon

MOI

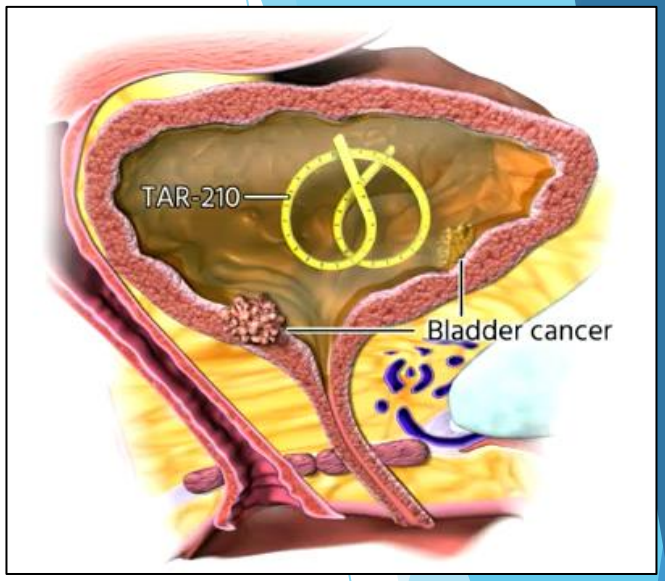
VOUS

Objectif (raisonnable) : Taux d’endormissement < 50%

Vessie

- TVNIM
  - TAR-210
  - THOR 2
- TVIM localisée
  - ABASCUS
  - NEMIO
- TVIM métastatique
  - CHECKMATE 901
  - EV 302/ KEYNOTE A39
  - DAD

TAR-210

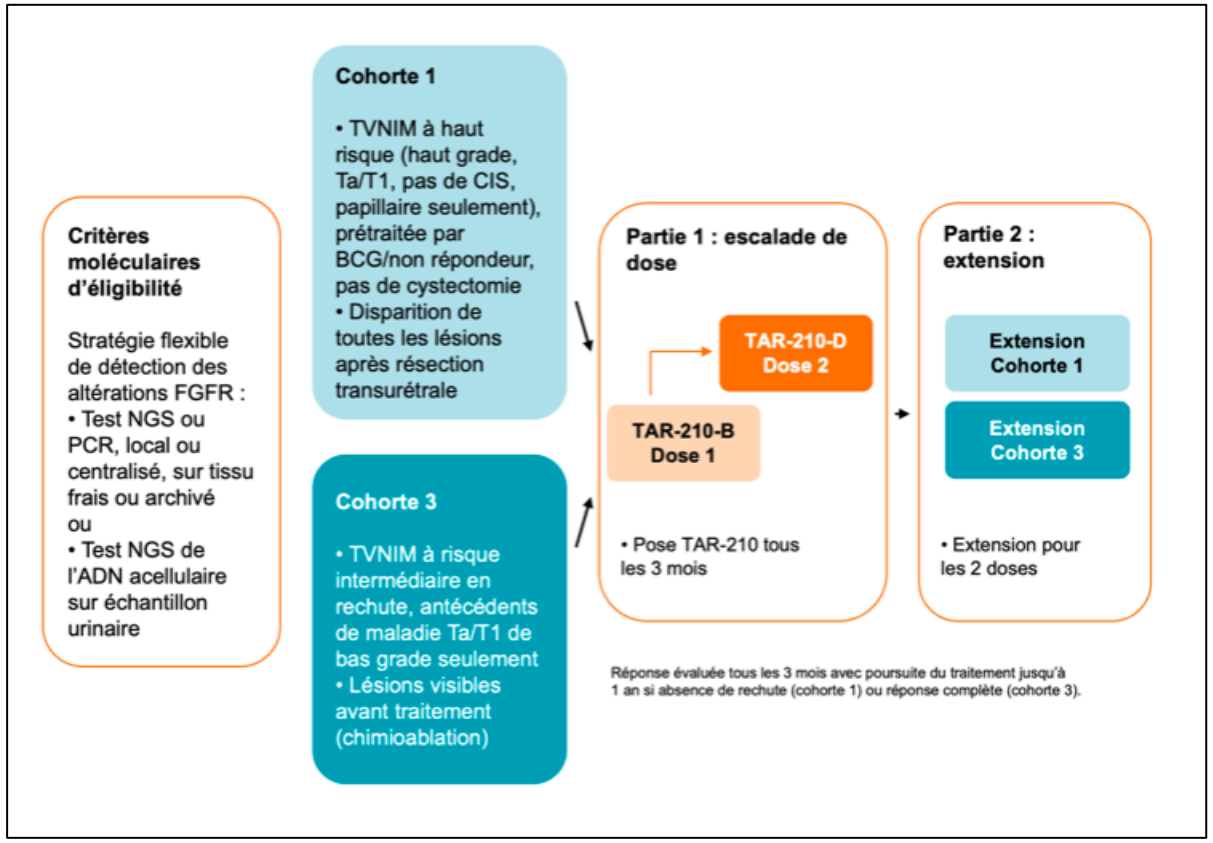


- Libération locale et continue d'Erdafitinib pendant 3 mois
- Erdafitinib : inhibiteur pan FGFR
  - Accès compassionnel
  - CU avancé/M+ avec altération de FGFR, post chimio à base de sel de platine et immunothérapie
- Altérations de FGFR :
  - 20% des carcinomes urothéliaux de vessie
  - 35% des CU des VES de haut grade
  - **50 à 80% des TVNIM**

Li *et al.*, 2016, Curr Urol Rep
Knowles *et al.*, 2015, Nat Rev Cancer

TAR-210

- Etude de phase 1 multicentrique, en ouvert, évaluant la sécurité, la pharmacocinétique et l'efficacité du TAR-210 chez les TVNIM altérés FGFR

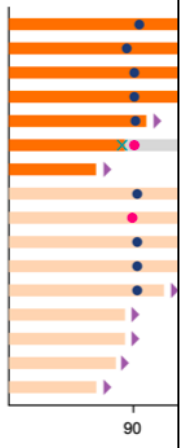


Vilaseca *et al.*, ESMO 2023

TAR-210

- Cohorte 1 : BCG réfractaire haut risque
- N = 16
- 82% sans récidive

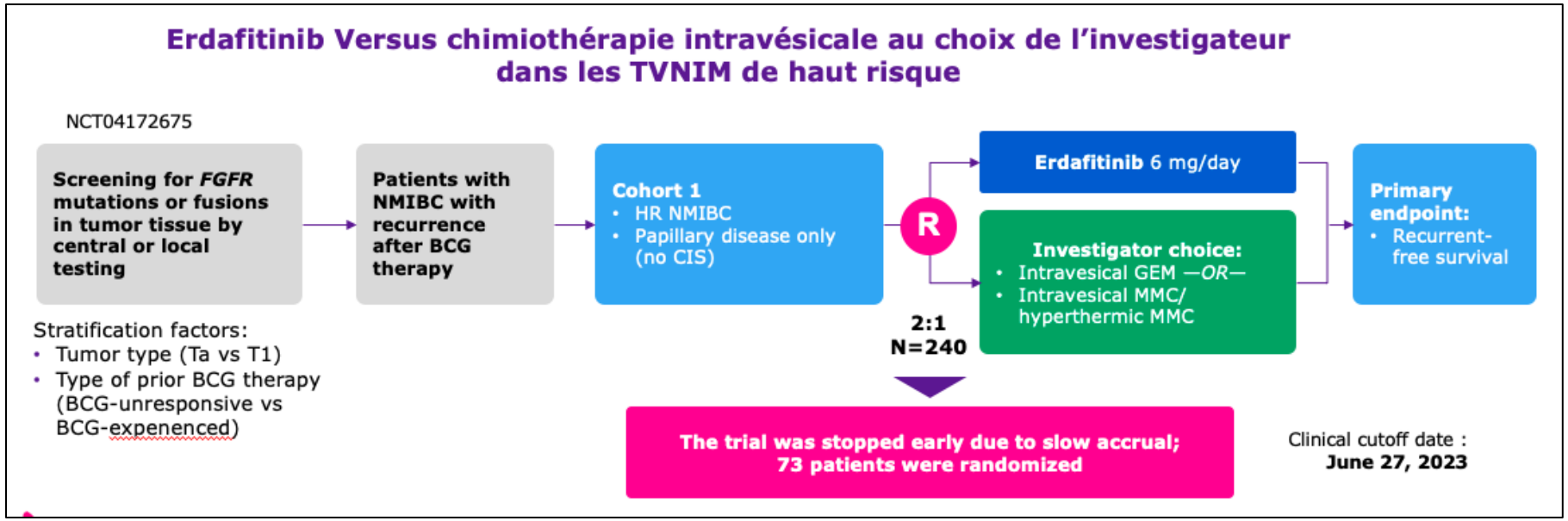
- Cohorte 3 : Rechute risque intermédiaire post BCG
- N = 27
- 87% de réponse complète



Patients with events, n (%)	Cohort 1 HR NIMBC TAR-210-B (n = 9)	Cohort 1 HR NIMBC TAR-210-D (n = 7)	Cohort 3 IR NIMBC TAR-210-B (n = 9)	Cohort 3 IR NIMBC TAR-210-D (n = 7)	All patients (n = 43)
≥ 1 AE	9 (100)	6 (86)	13 (93)	7 (54)	35 (81)
≥ 1 treatment-related	6 (67)	2 (29)	6 (43)	3 (23)	17 (40)
Haematuria	3 (33)	1 (14)	5 (36)	1 (8)	10 (23)
Dyruria	3 (33)	1 (14)	3 (21)	1 (8)	8 (19)
Micturition urgency	1 (11)	0	3 (21)	0	4 (9)
Urinary tract	0	0	2 (14)	1 (8)	3 (7)
≥ 1 treatment-related AE of grade ≥2	2 (22)	0	4 (29)	1 (8)	7 (16)

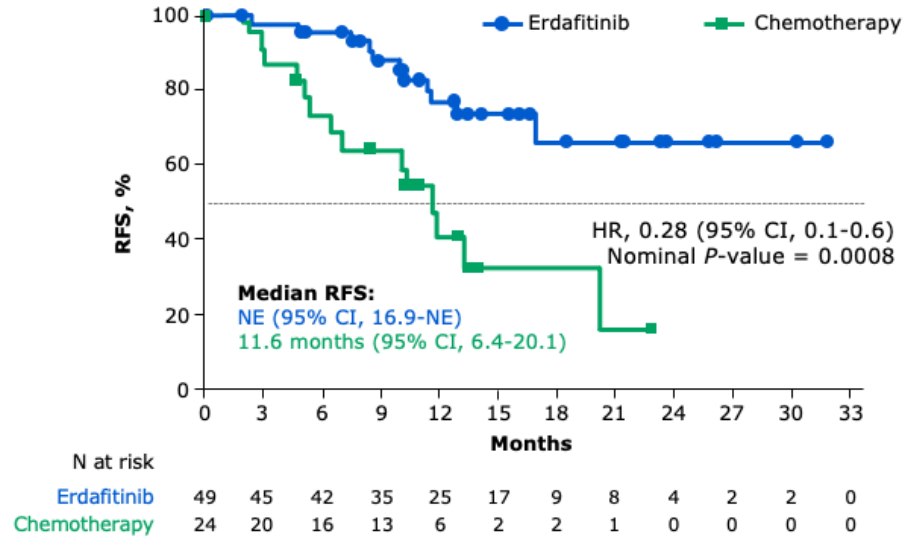
Vilaseca *et al.*, ESMO 2023

THOR 2



Catto *et al.*, ESMO 2023

THOR 2



- Avec un suivi median de 13,4 mois, la RFS médiane n'était pas atteinte dans le bras erdafitinib versus 11,6 mois dans le bras chimiothérapie
- Au cutoff clinique, 25 événements étaient survenus (11 dans le bras erdafitinib; 14 dans le bras chimiothérapie)

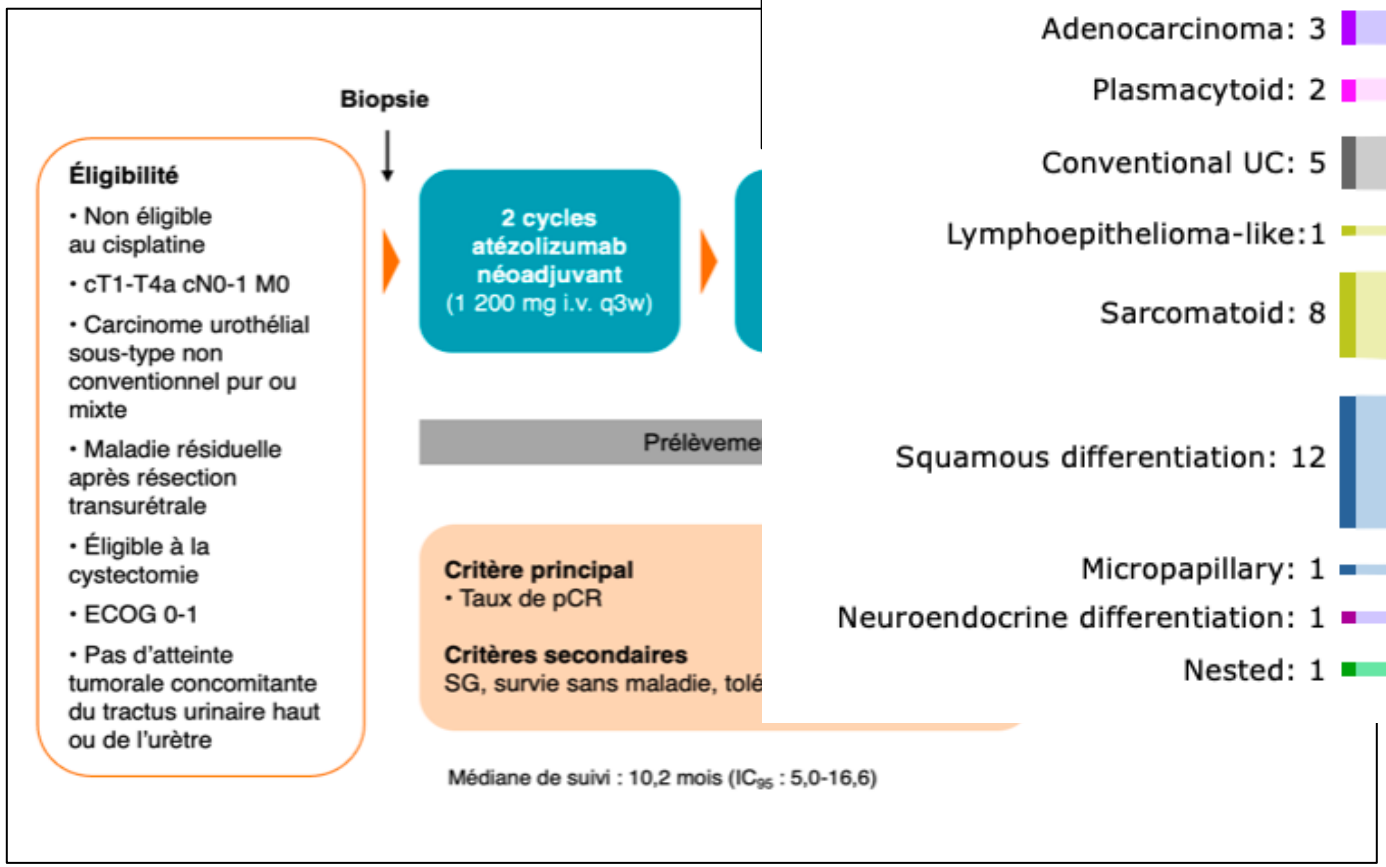
RFS rate (95% CI), %	Erdafitinib (n=49)	Chemotherapy (n=24)
At 6 months	**96 (84-99)**	**73 (50-87)**
At 12 months	**77 (60-87)**	**41 (19-62)**

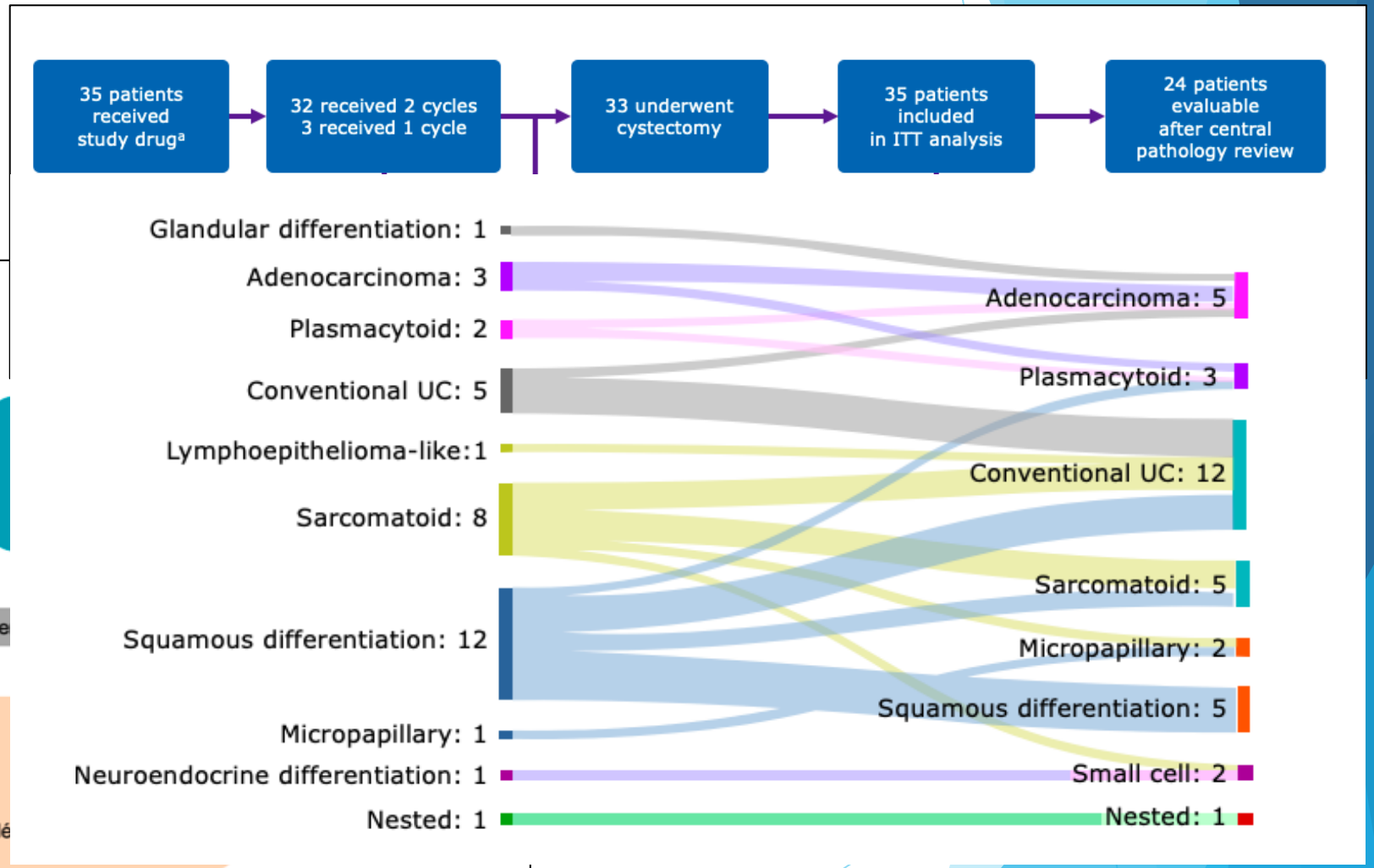
- DFS à 1 an
  - > Pembro (43.5 % - KN 057) et Atezo (53% - SWOGS1605)

Catto *et al.*, ESMO 2023

ABASCUS

- Phase II
- Carcinomes non urothéliaux

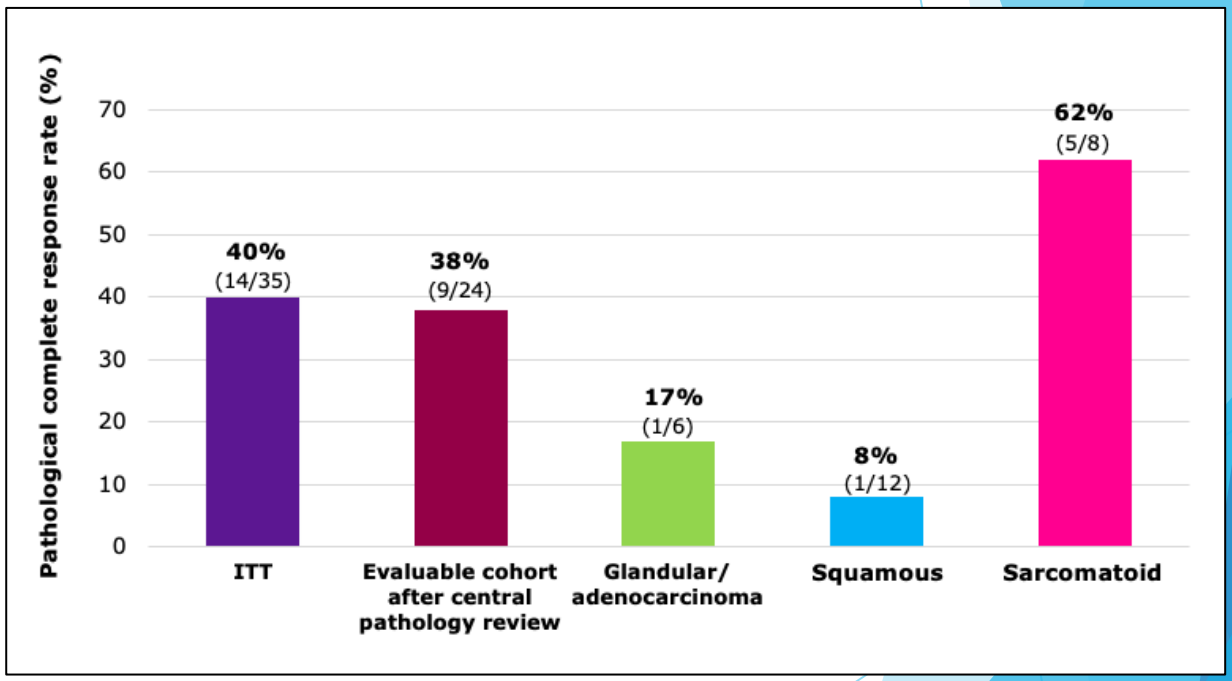




Szabados *et al.*, ESMO 2023

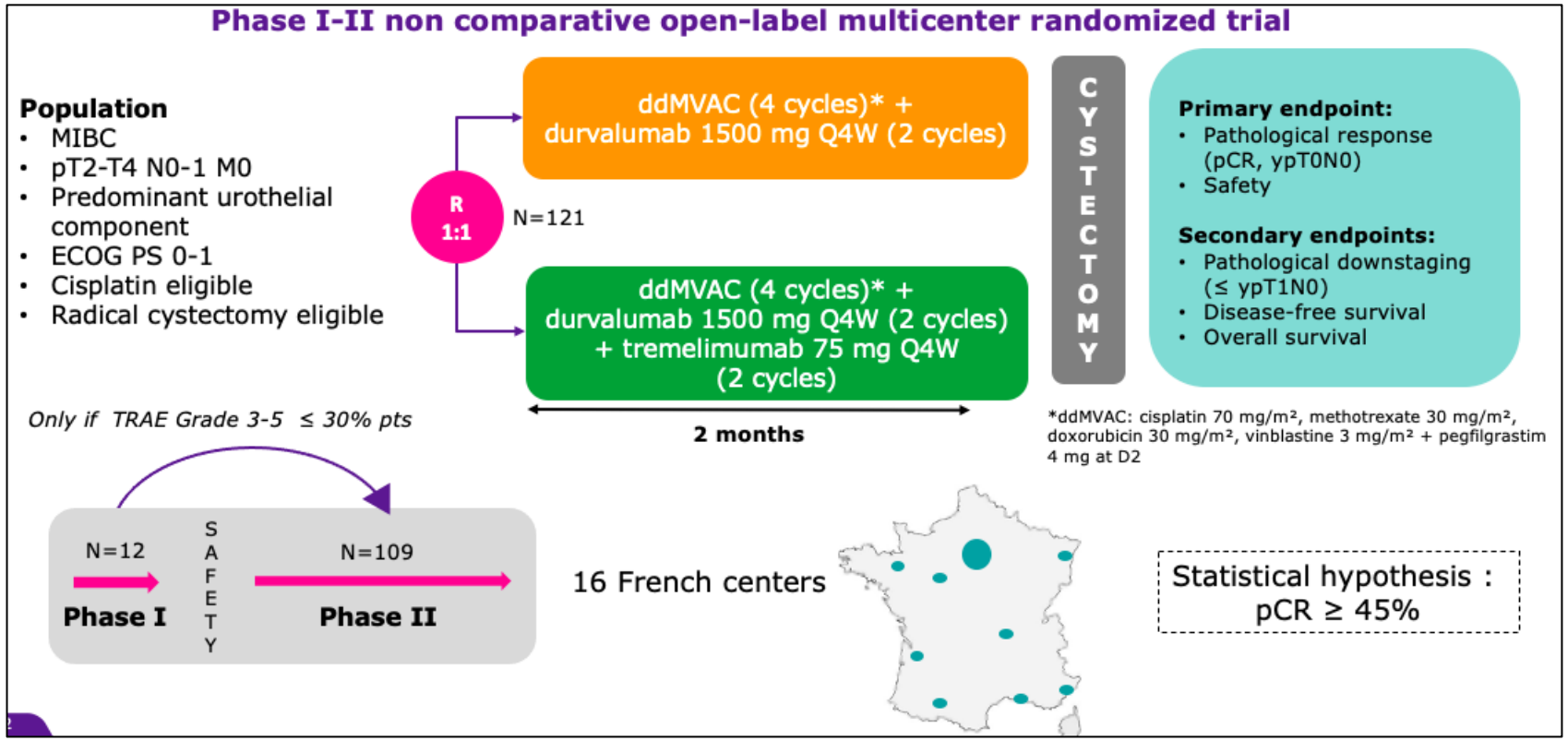
ABASCUS

- Relecture centralisée +++
- Intérêt potentiel immuno pour les tumeurs sarcomatoïdes
- Nécessité d'études dédiées pour ces sous populations histologiques



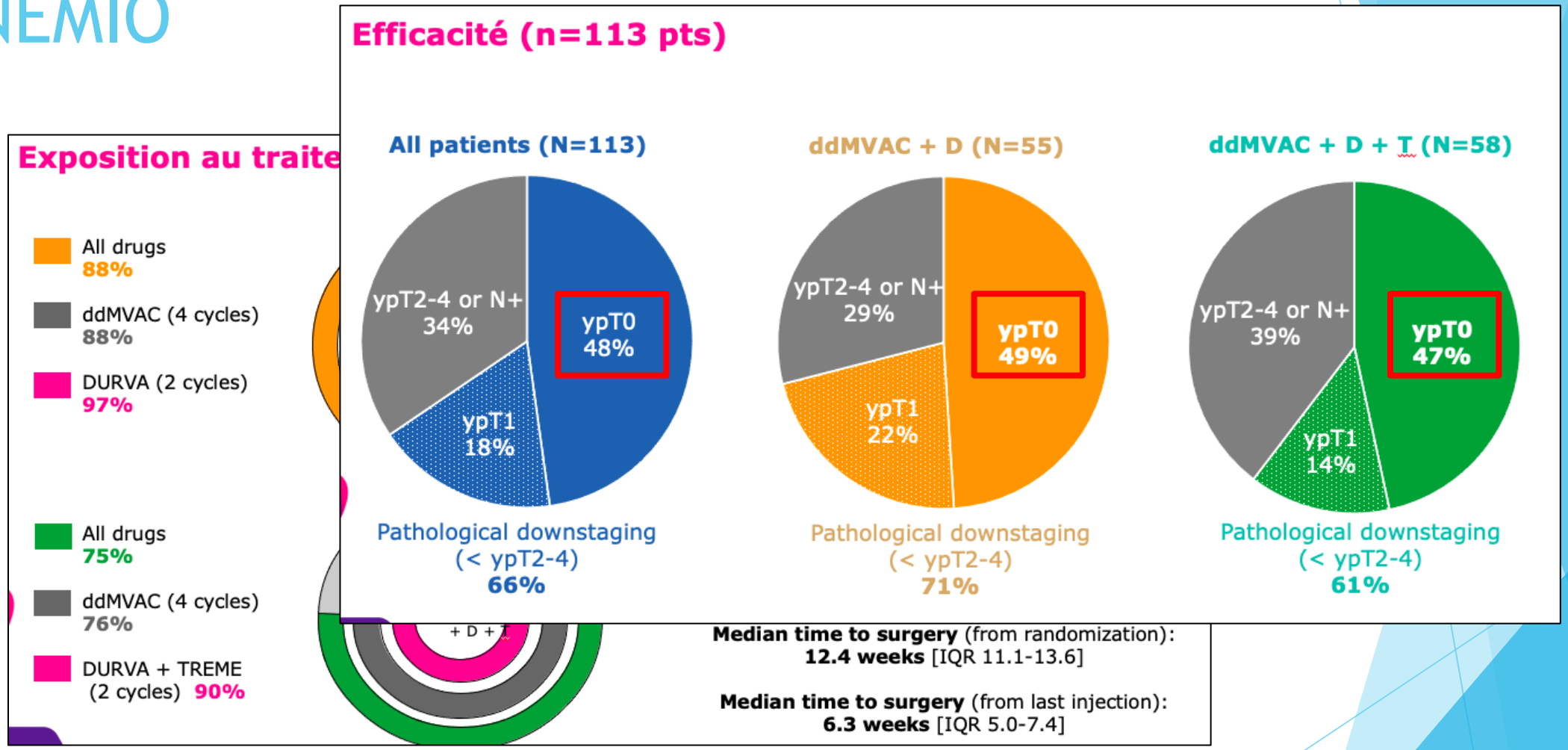
Szabados *et al.*, ESMO 2023

NEMIO



Thibault *et al.*, ESMO 2023

NEMIO



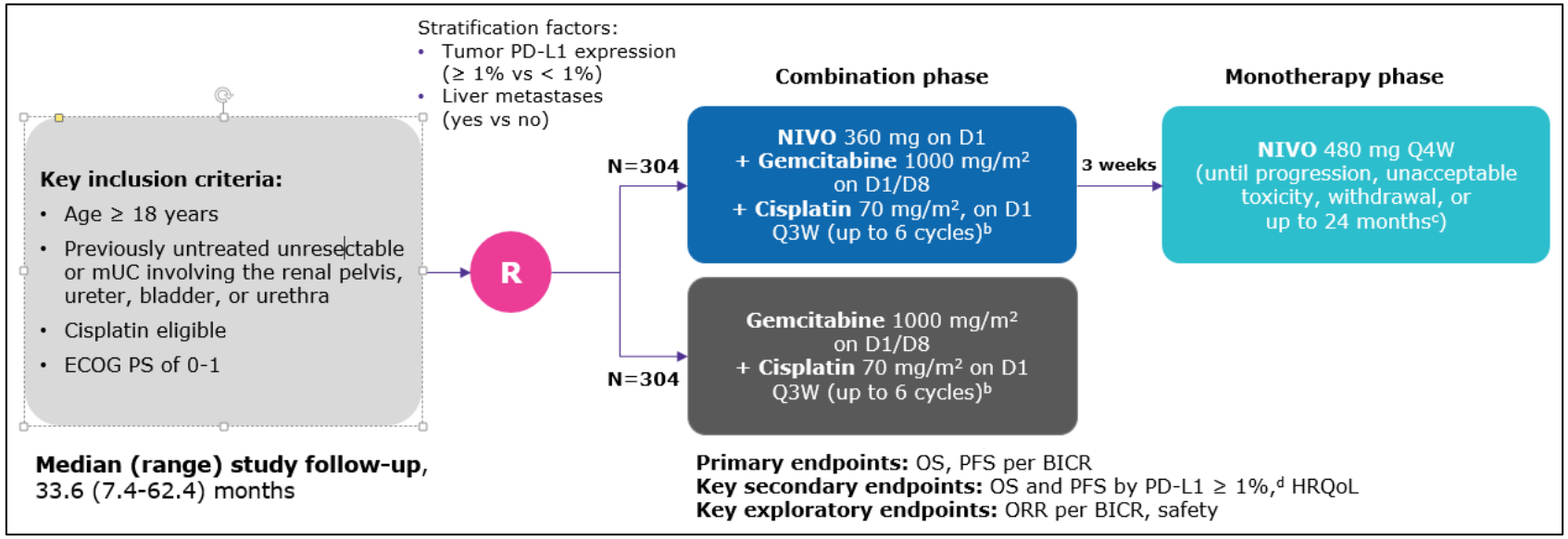
Faisabilité (et absence de tox majeure)
Mais taux pCR assez proche du MVACdd

Thibault *et al.*, ESMO 2023

CHECKMATE 901

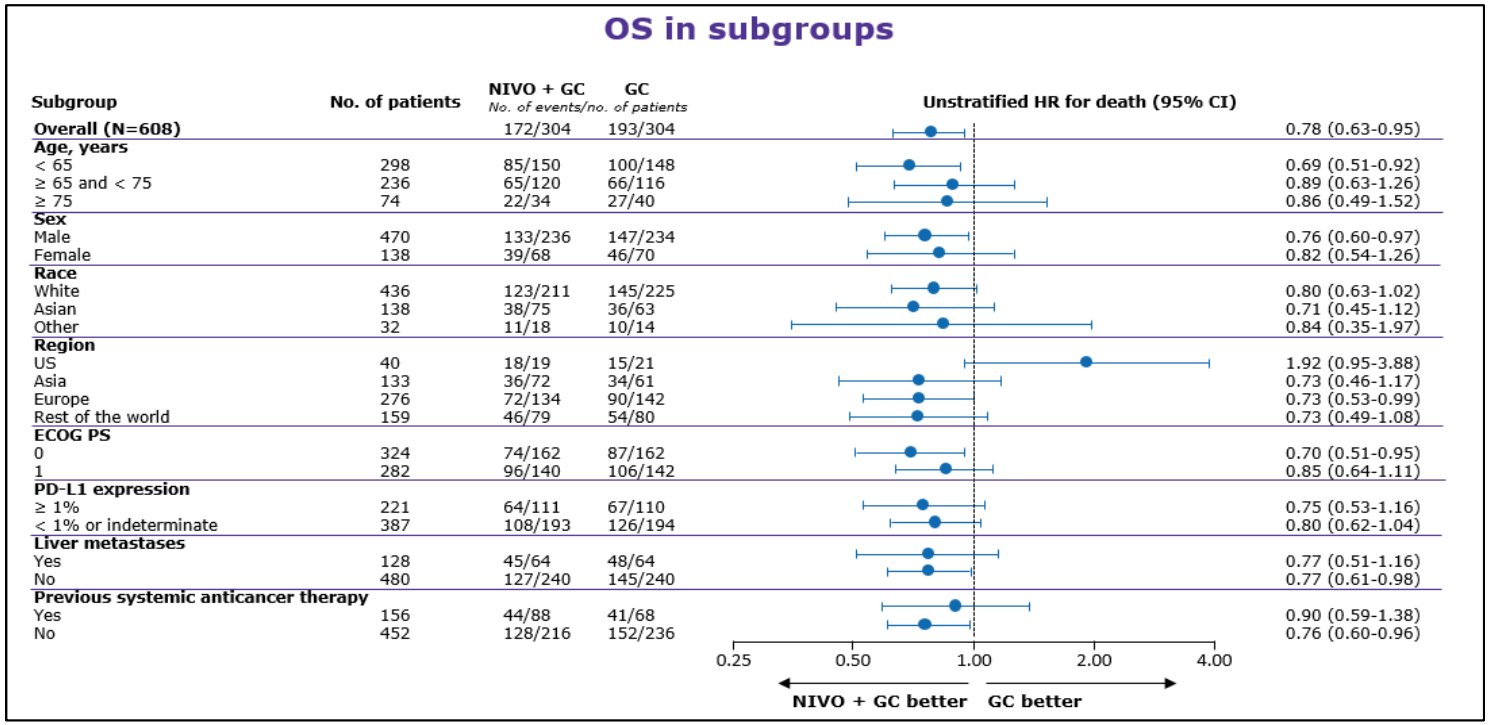
Tumor type at initial diagnosis, n (%)		
Urinary bladder	235 (77)	219 (72)
Renal pelvis	33 (11)	44 (24)
Other	36 (12)	41 (13)
Tumor PD-L1 expression, n (%)[b]		
≥1%	111 (37)	110 (36)
< 1% or undeterminate[c]	193 (63)	194 (64)
Liver metastases, n (%)[b]	64 (21)	64 (21)

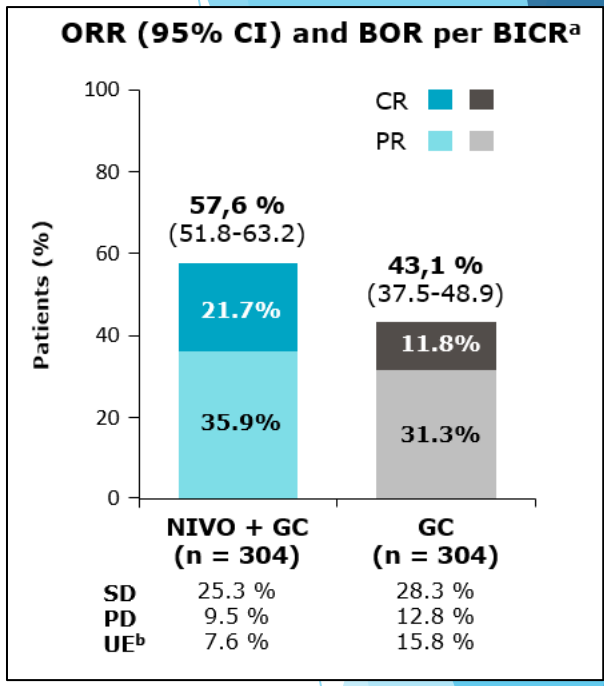
- Phase III randomisée



Van der Heijden *et al.*, ESMO 2023

CHECKMATE 901





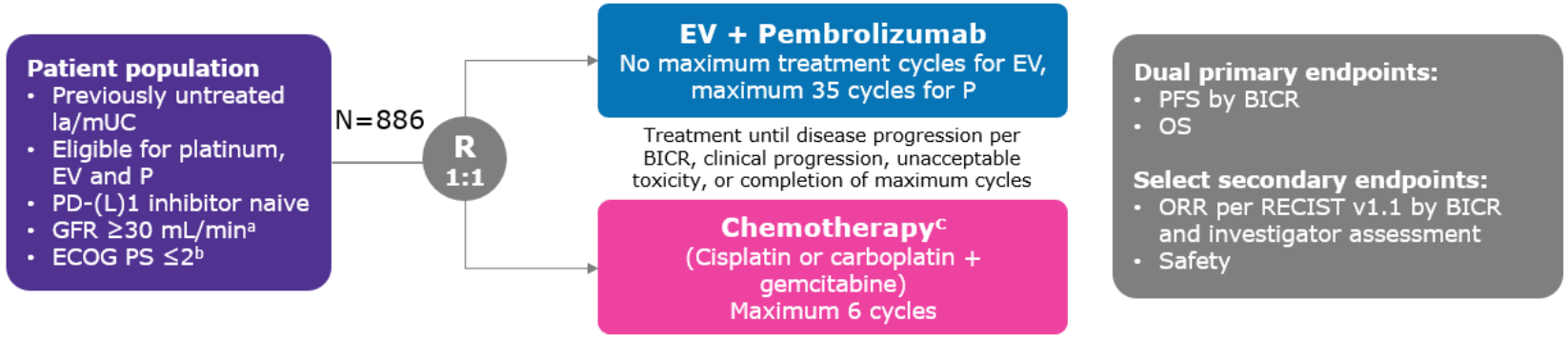
- Résultats positifs en survie globale… mais pas le bon timing …

- mPFS 7,9 vs 7,6 mois
- PFS 2 ans : 23,9% vs 9,6%
- Pas de signal de tox

Van der Heijden *et al.*, ESMO 2023

EV-302 / KN-A39

EV-302/KEYNOTE-A39 (phase III) : Design



- Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)
- Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1
- Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final.

Powles *et al.*, ESMO 2023

EV-302 / KN-A39

Caractéristiques des patients

	EV+P (N = 442)	Chemotherapy (N = 444)
Male sex, n (%)	344 (77,8)	336 (75,7)
Age (years), median (range)	69,0 (37,87)	69,0 (22,91)
Race, n (%)		
White	308 (69,7)	290 (65,3)
Asian	99 (22,4)	92 (20,7)
Geographic location, n (%)		
North America	103 (23,3)	85 (19,1)
Europe	172 (38,9)	197 (44,4)
Rest of the world	167 (37,8)	162 (36,5)
ECOG PS, n (%)		
0	223 (50,5)	215 (48,4)
1	204 (46,2)	216 (48,6)
2	15 (3,4)	11 (2,5)
Primary tumor location, n (%)		
Upper tract	135 (30,5)	104 (23,4)
Lower tract	305 (69,0)	339 (76,4)

	EV+P (N = 442)	Chemotherapy (N = 444)
Cisplatin eligible[a], n (%)	240 (54,3)	242 (54,5)
Metastatic category, n (%)		
Visceral metastases	318 (71,9)	318 (71,6)
Bone	81 (18,3)	102 (23,0)
Liver	100 (22,6)	99 (22,3)
Lung	170 (38,5)	157 (35,4)
Lymph node only disease	103 (23,3)	104 (23,4)
PD-L1 expression[b], n/N (%)		
High (CPS ≥ 10)	254/438 (58,0)	254/439 (57,9)
Low (CPS < 10)	184/438 (42,0)	185/439 (42,1)

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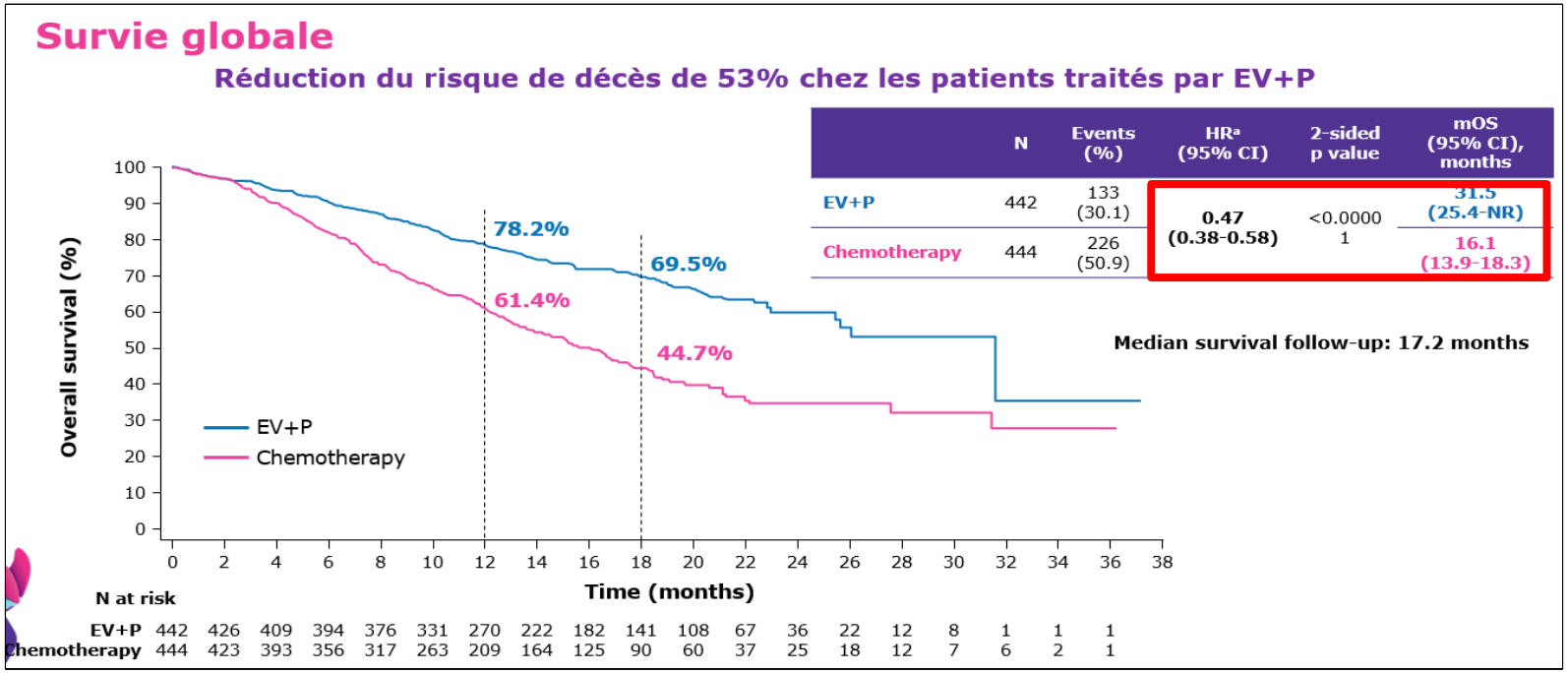
EV-302 / KN-A39



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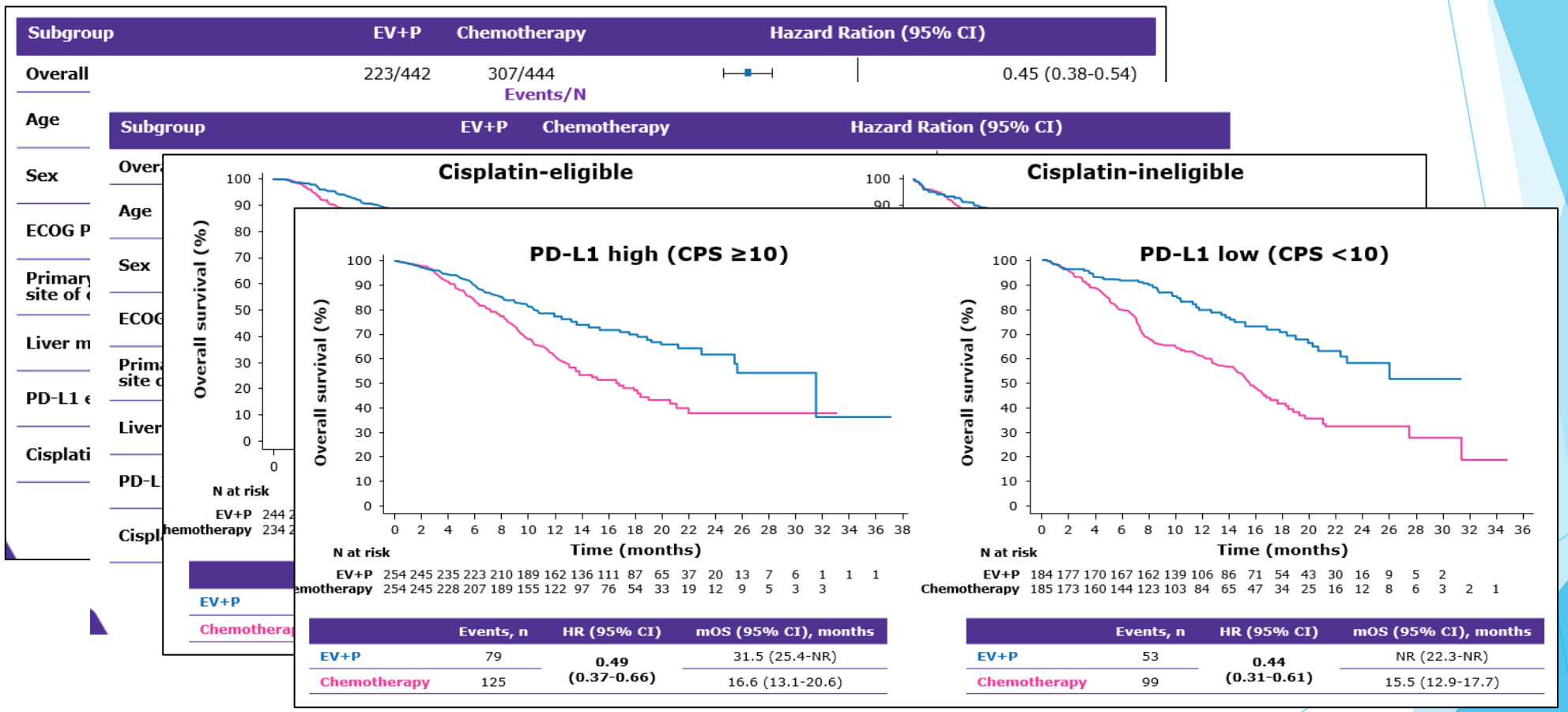
EV-302 / KN-A39



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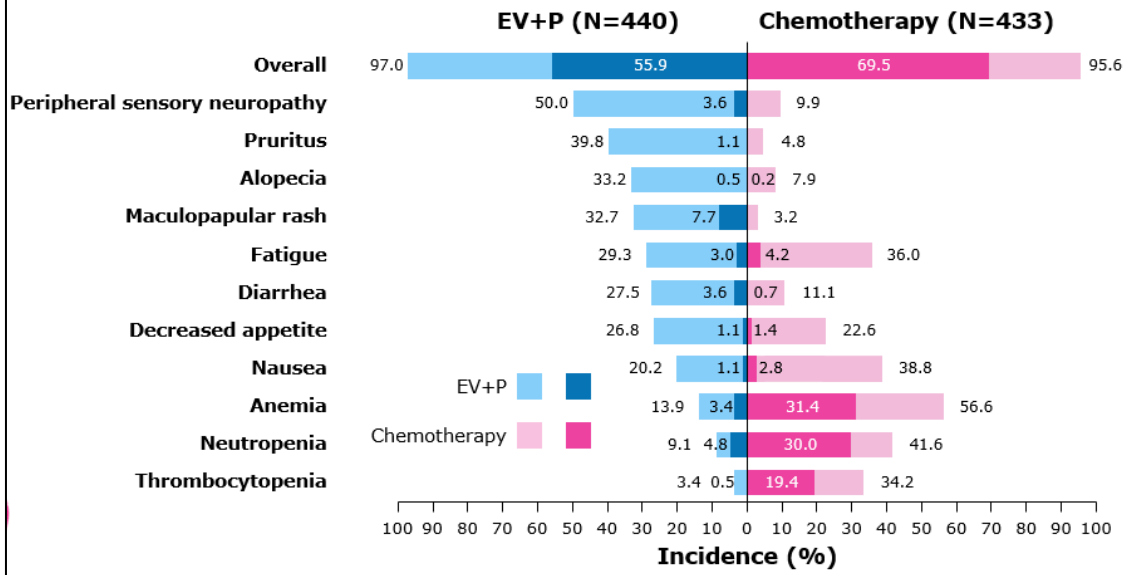
EV-302 / KN-A39

L'incidence des EI de grade ≥3 était de 56% avec EV + P et de 70% avec la chimiothérapie



Evénements graves :

- 122 (27.7%) EV+P
- 85 (19.6%) chimiothérapie

Evénements conduisant au décès (selon l'investigateur) :

EV+P: 4 (0.9%)

- Asthénie
- Diarrhée
- Maladie pulmonaire à médiation immunitaire
- Syndrome de défaillance multiviscéra

Chimiothérapie: 4 (0.9%)

- Neutropénie fébrile
- Infarctus du myocarde
- Sepsis neutropénique
- Sepsis

Le nombre median de cycles était de 12.0 (1-46) pour EV+P et de 6.0 (1-6) pour la chimiothérapie

Powles *et al.*, ESMO 2023

EV-302 / KN-A39

- Traitements ultérieurs

59 % des patients du bras chimiothérapie ont reçu un anti-PD-1/L1

	EV+P (N=442) n (%)	Chemotherapy (N=444) n (%)
First subsequent systemic therapy[a]	128 (28,9)	294 (66,2)
Platinum-based therapy	110 (24,9)	17 (3,8)
PD-1/L1 inhibitor-containing therapy	7 (1,6)	260 (58,6)
Maintenance therapy	0	143 (32,2)
Avelumab maintenance	0	135 (30,4)
PD-1/L1 inhibitor-containing therapy following progression	7 (1,6)	117 (26,4)
Other	11 (2,5)	17 (3,8)

[a]144 (32,6%) patients in the EV+P arm remain on treatment at time of analysis

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EV-302 / KN-A39

- Nouveau vraisemblable standard en L1
- Nouveau profil de tolérance → adaptabilité !!!

- Questionnements :
  - Faudra t-il sélectionner les patients ? Et comment ?
  - Place persistante pour la chimio en L1 ? Pour qui ?
  - Quid du bénéfice par rapport aux patients ayant reçu l'avélumab dans le bras contrôle ? (sous utilisation de l'Avélumab - 77% de patients étaient éligibles)

DAD

- Association d'ADCs
- EV + SG
- Patients lourdement pré traités

	Target	Payload	Toxicities
EV	Nectin-4	Monomethyl Auristatin E (MMAE)	Neuropathy Rash Hyperglycemia
SG	Trop2	SN38 (Irinotecan Metabolite)	Myelosuppression Diarrhea

N	23
Histology	
Mixed urothelial	7 (30%)
Pure urothelial	16 (70%)
Number of lines of prior therapy	
1	1 (4%)
2	11 (48%)
3-5	11 (48)
Prior therapy	
Immunotherapy	22 (96%)
Platinum Based chemotherapy	22 (96%)
Metastatic sites	
Bone	6 (26%)
Kidney	3 (13%)
Liver	6 (26%)
Lung	5 (22%)
Lymph nodes	17 (74%)

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DAD

- Med follow up : 14.9 mois
- ORR = 70%
- PFS 12 mois : 41%
- OS 12 mois : 86%
- Toxicité manageable

	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	12 (52,2%)	6 (26,1%)	2 (8,7%)	-
Anemia	4 (17,4%)	5 (21,7%)	8 (34,8%)	-
Neutrophil count decreased	3 (13,0%)	5 (21,7%)	4 (17,4%)	4 (17,4%)
Fatigue	8 (34,8%)	5 (21,7%)	2 (8,7%)	-
Alopecia	3 (13,0%)	11 (47,8%)	-	-
Peripheral sensory neuropathy	5 (21,7%)	8 (34,8%)	-	-
Nausea	7 (30,4%)	2 (8,7%)	1 (4,3%)	-
Alanine aminotransferase increased	8 (34,8%)	2 (8,7%)	-	-
Aspartate aminotransferase increased	9 (39,1%)	1 (4,3%)	-	-
Weight loss	3 (13,0%)	4 (17,4%)	-	-

	Grade 1	Grade 2	Grade 3	Grade 4
Alkaline phosphatase increased	6 (26,1%)	1 (4,3%)	-	-
Rash	6 (26,1%)	1 (4,3%)	-	-
Dry eye	4 (17,4%)	2 (8,7%)	-	-
Constipation	5 (21,7%)	1 (4,3%)	-	-
Dysgeusia	5 (21,7%)	1 (4,3%)	-	-
Watering eye	5 (21,7%)	1 (4,3%)	-	-
Hypomagnesemia	4 (17,4%)	1 (4,3%)	-	-
Pruritus	1 (4,3%)	4 (17,4%)	-	-
Hypophosphatemia	1 (4,3%)	3 (13,0%)	-	-
Urinary tract infection	-	1 (4,3%)	3 (13,0%)	-
Anorexia	2 (8,7%)	1 (4,3%)	1 (4,3%)	-

*One grade 5 pneumonitis possibly related to EV
Table displays toxicities for a10% of the experienced patients regardless of dose level.

**Among three patients with complete response, two had lymph node lesions and the sum of lesions was not zero for those achieving a complete response

	Overall (N=23)	DL1 (N=9)	DL2 (N=8)	DL3 (N=6)
Objective Response Rate, % (95% CI)	70 (47-87)	78 (40-97)	75 (35-97)	50 (12-88)
Best Overall Response				
CR	3	1	1	1
PR	13	6	5	2
SD	3	1	1	1
PD	3	1	1	1
NE	1	0	0	1
Total	23	9	8	6

DL=dose level; CI=confidence interval; CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=not evaluated

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Prostate

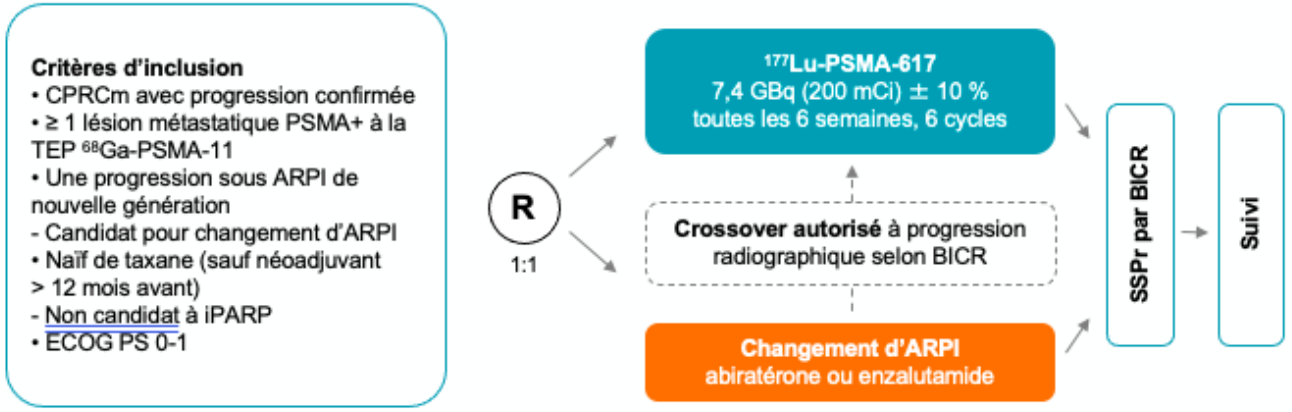
- PSMAfore

PSMAfore

Schéma de l'étude

- Étude de phase III randomisée en ouvert comparant ^{177}Lu-PSMA et changement d'hormonothérapie chez des patients atteints d'un cancer de la prostate métastatique progressant sous hormonothérapie de nouvelle génération (ARPI)

Schéma de l'étude



ARPI : inhibiteur de la voie du récepteur aux androgènes.

Facteurs de stratification
• Contexte de l'administration d'ARPI (sensible ou résistant à la castration)
• Score de douleur maximale BPI-SF (0-3 versus > 3)

- Critère principal : SSP radiographique (SSPr)
- Analyse de la SG ajustée sur le crossover (84 % des patients du bras changement d'ARPI (cARPI) ont reçu du Lu-PSMA à progression)

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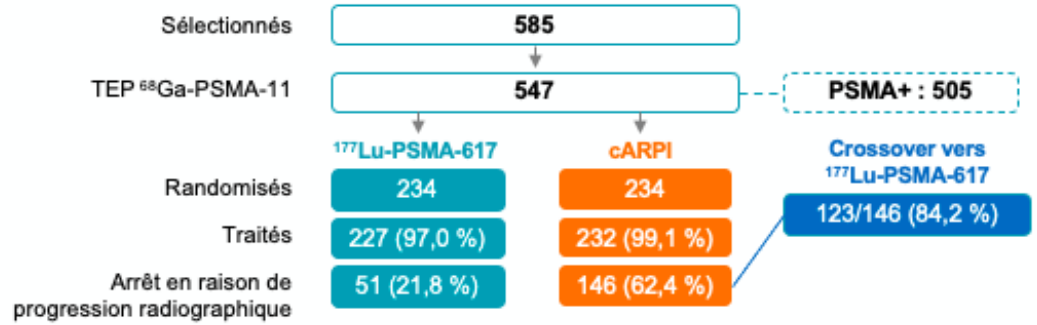
PSMAfore

Caractéristiques et disposition des patients

	^{177}Lu-PSMA-617 (n = 234)	cARPI (n = 234)
Âge, années, médiane (range)	71 (43-94)	72 (53-91)
ECOG PS, n (%)		
0	146 (62,4)	115 (49,1)
1	86 (36,8)	114 (48,7)
Score de Gleason 8-10 (%)	136 (58,1)	107 (45,7)
PSA, médiane (range), pg/L	18,4 (0-1 197)	14,9 (0-4 224)
Hémoglobine, médiane (range), g/L	128,0 (88-155)	129,0 (88-156)
Phosphatases alcalines, médiane (range), IU/L	100,0 (36-1 727)	103,5 (28-1 319)
Site des métastases, n (%)		
Foie	13 (5,6)	7 (3,0)
Ganglions lymphatiques	76 (32,5)	74 (31,6)
Os	205 (87,6)	203 (86,8)
ARPI préalable, n (%)		
Abiratérone	119 (50,9)	130 (55,6)
Enzalutamide	94 (40,2)	84 (35,9)
Autre	21 (9,0)	20 (8,5)



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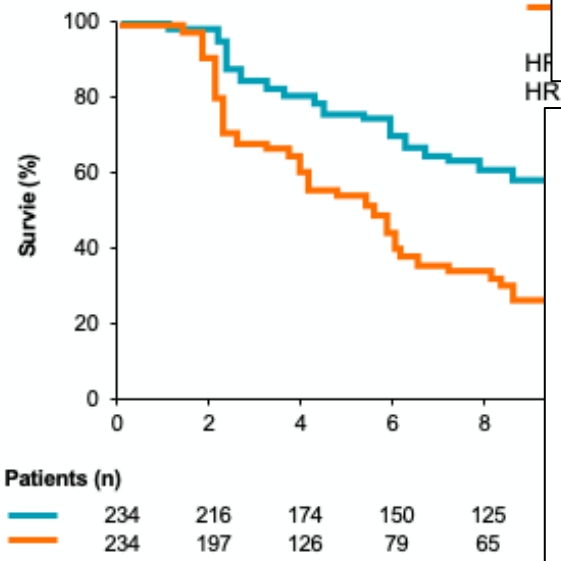
PSMAfore

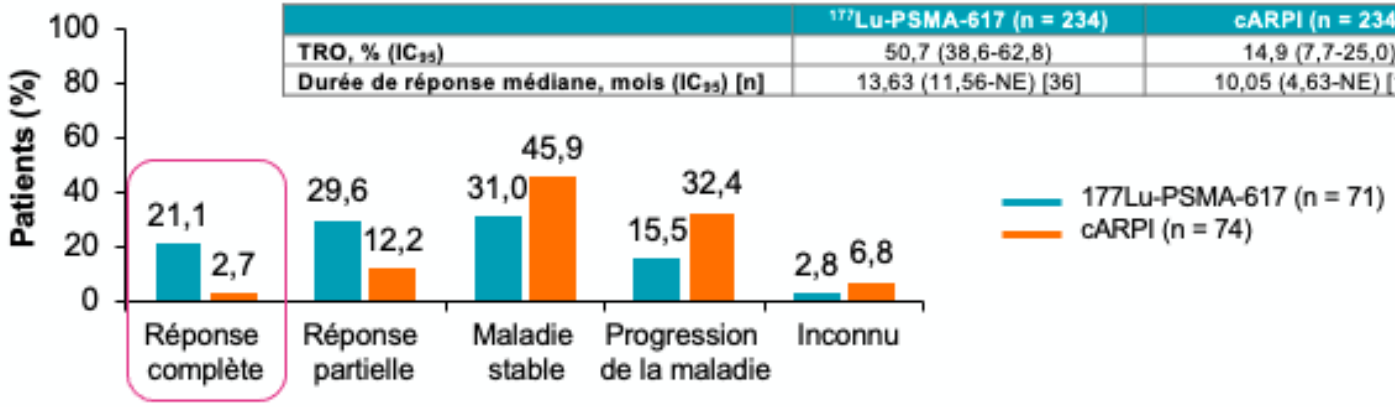
Résultats : critère principal (SSPr)



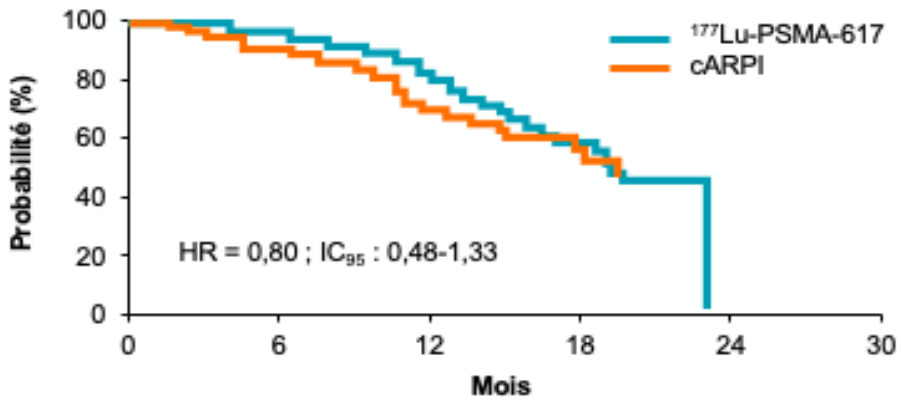
HR actualisé = 0,43 ; IC_{95} : 0,33-0,54

Taux de réponse

	^{177}Lu-PSMA-617 (n = 234)	cARPI (n = 234)
TRO, % (IC_{95})	50,7 (38,6-62,8)	14,9 (7,7-25,0)
Durée de réponse médiane, mois (IC_{95}) [n]	13,63 (11,56-NE) [36]	10,05 (4,63-NE) [11]



Survie globale (2e analyse intermédiaire, ajustement sur crossover)



	n	Médiane de suivi, mois	SG médiane, mois
^{177}Lu-PSMA-617	234	12,72	19,25 (16,95-NE)
cARPI	234	13,08	19,55 (14,95-NE)

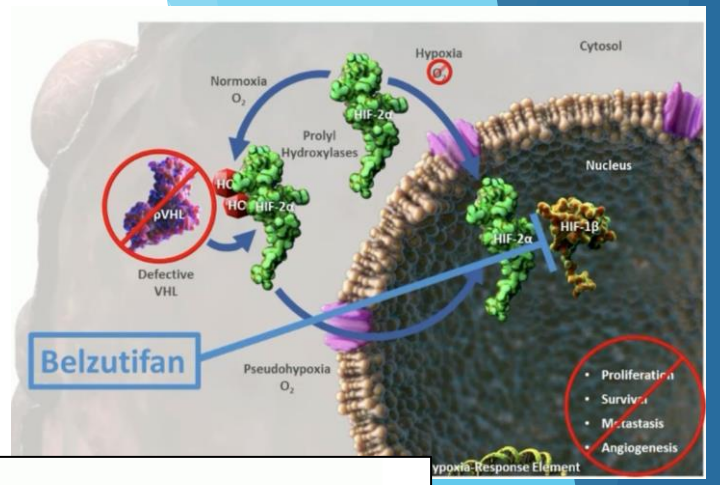
Crossover : 123/146 (84,2 %)

Sartor *et al.*, ESMO 2023

Rein

- LITESPARK-005
- LITESPARK-003

LITESPARK-005



Population:

- Cancer du rein à cellules claires métastatique
- Prétraité par 1-3 lignes de traitement (incluant IO et antiangiogénique)
- Karnovsky performance status ≥ 70
- Maladie mesurable (RECIST v1.1)

Stratification

Score IMDC (1 vs 2-3 vs 3-6)

Nb antiangiogéniques 1 vs 2-3

Critère principal :

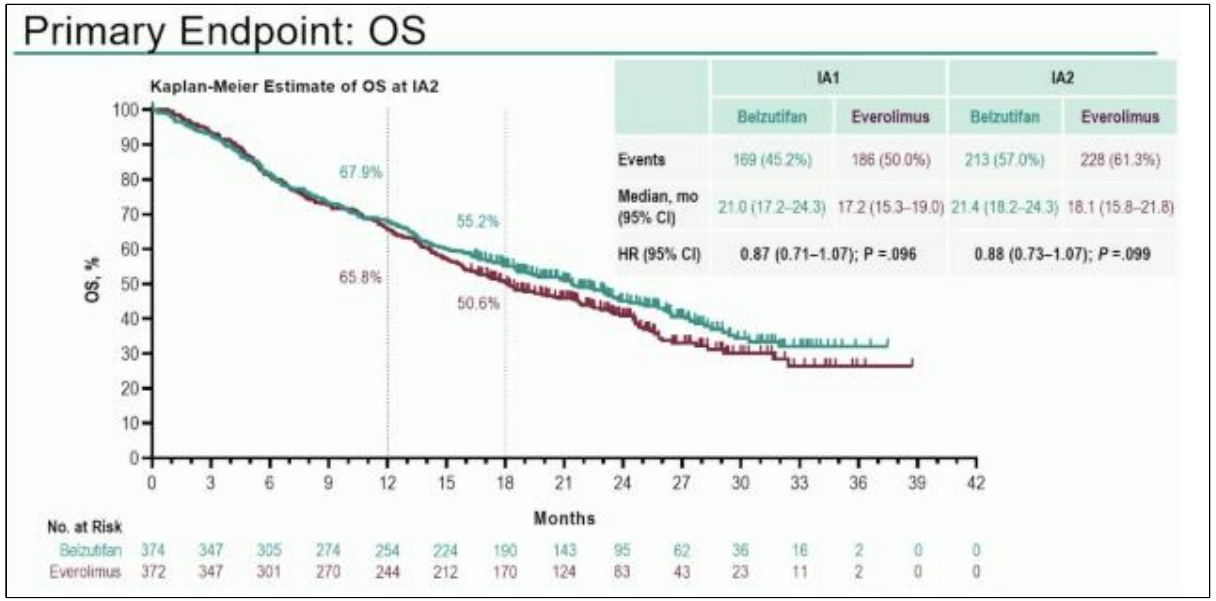
- OS
- PFS

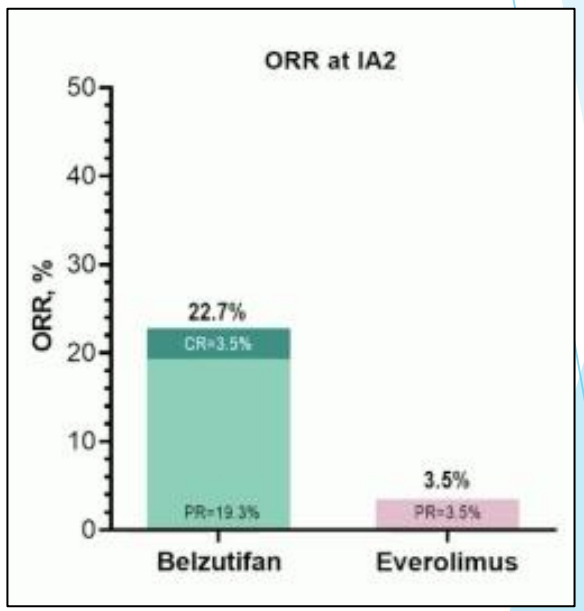
Baseline Characteristics

	Belzutifan (N = 374)	Everolimus (N = 372)
Age, median (range), yrs	62 (22–90)	63 (33–87)
Male	79.4%	76.3%
KPS score[a]		
90/100	63.6%	64.5%
70/80	36.1%	35.2%
IMDC risk categories		
Favorable	21.1%	22.3%
Intermediate	66.6%	65.6%
Poor	12.3%	12.1%
Sarcomatoid features		
Yes	11.2%	8.3%
No/Unknown/Missing	88.8%	91.7%
Prior nephrectomy	69.8%	69.6%
# Prior VEGF/VEGFR-TKIs		
1	50.0%	51.1%
2-3	50.0%	48.9%
# Prior lines of therapy[b]		
1	12.3%	14.0%
2	42.0%	44.6%
3	45.2%	40.3%

Albiges *et al.*, ESMO 2023

LITESPARK-005



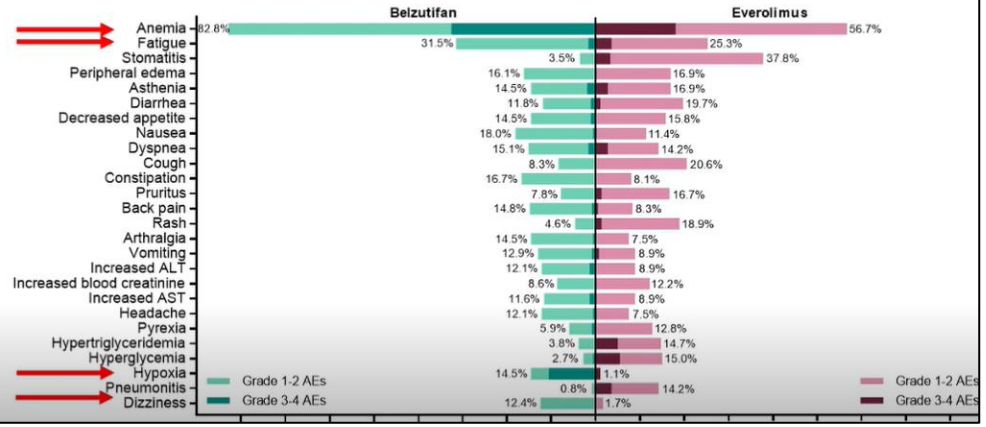


Albiges *et al.*, ESMO 2023

LITESPARK-005

	Belzutifan (N = 372)	Everolimus (N = 360)
Median duration of therapy, mo (range)	7.6 (0.1–35.8)	3.9 (0.0–33.2)
All-cause AEs, n (%)	369 (99.2%)	357 (99.2%)
Grade ≥3	230 (61.8%)	225 (62.5%)
Serious	157 (42.2%)	137 (38.1%)
Led to discontinuation	22 (5.9%)	53 (14.7%)
Led to death	13 (3.5%)	19 (5.3%)
Treatment-related AEs, n (%)	331 (89.0%)	322 (89.4%)
Grade ≥3	144 (38.7%)	142 (39.4%)
Serious	49 (13.2%)	47 (13.1%)
Led to death	1 (0.3%)[a]	2 (0.6%)[b]

Tolérance



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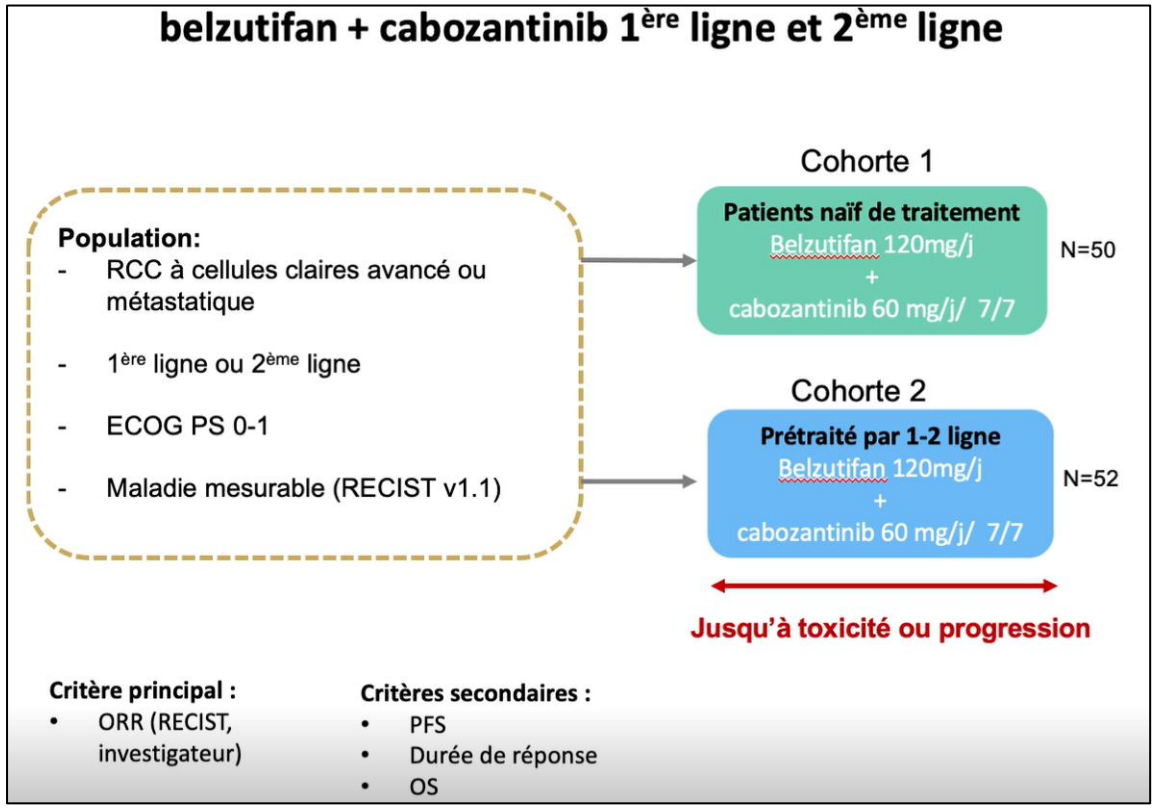
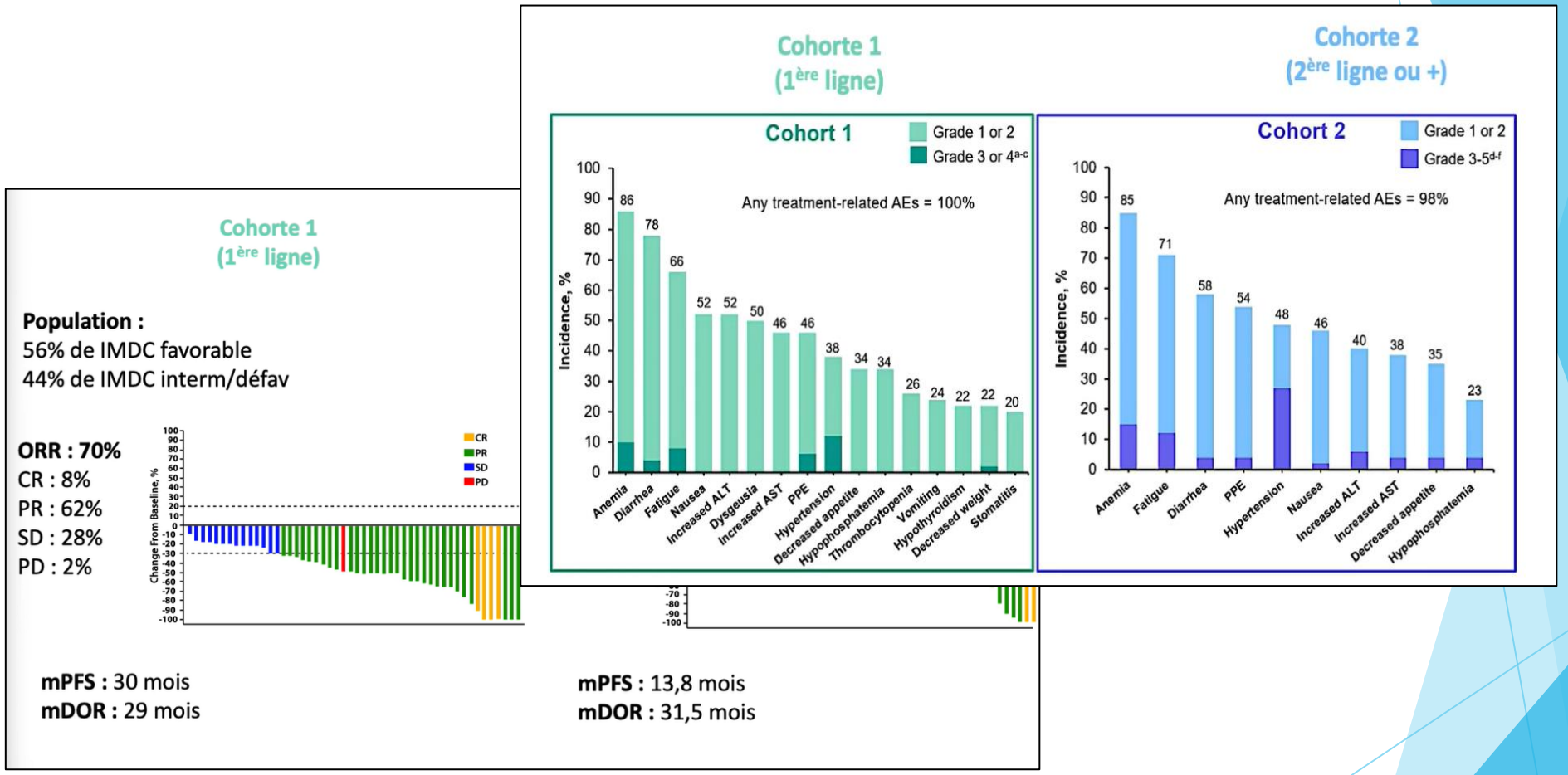
LITESPARK-003



Choueiri *et al.*, ESMO 2023

LITESPARK-003



Choueiri *et al.*, ESMO 2023

Take Home Messages

- Vessie :
  - Practice changing : EV + Pembrolizumab → L1 des TVIM LA/M
  - Place potentielle de l'immuno pour les TVIM localisées de sous type sarcomatoïde
  - Intérêt potentiel de l'Erdafitinib pour les TVNIM avec altération de FGFR
- Prostate :
  - Activité du PSMA-Lu en mCRPC chimio naïf
- Rein :
  - Positionnement futur du Belzutifan en monothérapie… et probablement en association avec TKI ?

Post ESMO 2023
Onco urologie

Courèche KADERBHAI
Oncologue médical
CGFL - Dijon