ONCOLOGIE UROLOGIQUE DE LA VESSIE : TVIM

06/12/2023

Niort

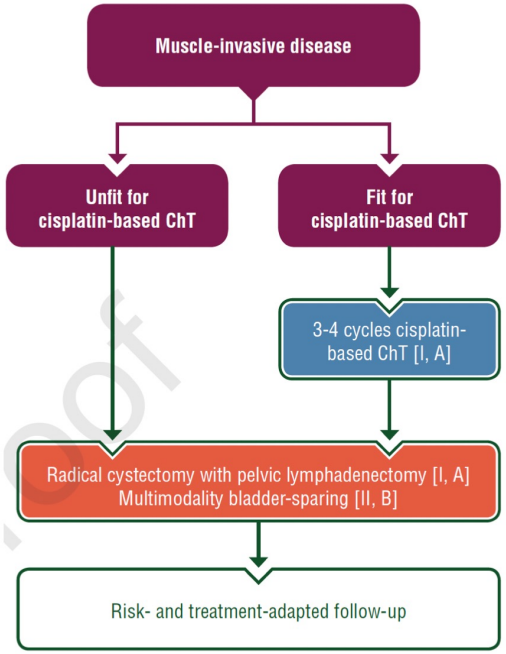
Mathilde Small

Rétrospectives et Perspectives en Onco-urologie 2023

Cancer de vessie : péri-opératoire

Péri-opératoire

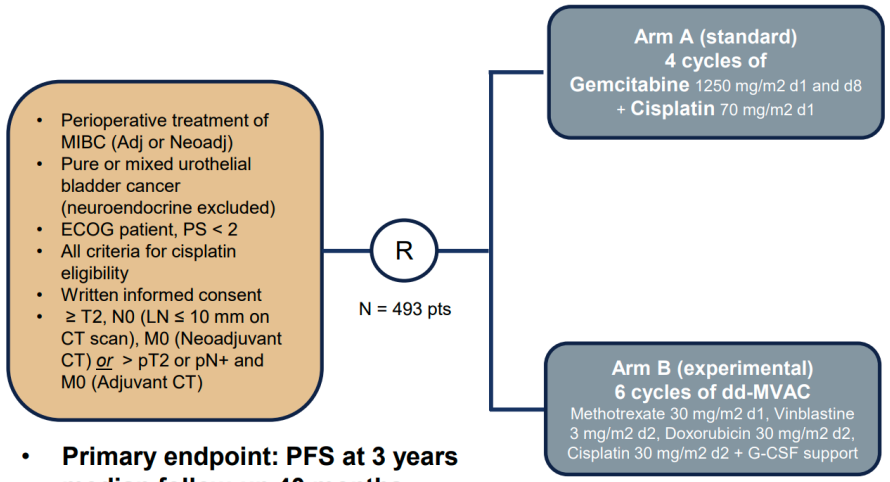
Chimiothérapie recommandation ESMO



- **40-67%** of patients with pT3-T4a or lymph node-positive disease relapse after RC alone, with a poor 5-year OS (25-30%)
- **Only 12-13%** of MIUC patients undergoing radical cystectomy receive neoadjuvant chemotherapy, despite current guidelines
- **50%** of patients who receive neoadjuvant chemotherapy have residual high-risk disease (≥pT2) with an associated median survival of 3.4 years
- **50%** of patients are ineligible for cisplatin-based adjuvant chemotherapy and there is no standard of care for these patients

Péri-opératoire

Quel régime de chimiothérapie : mise à jour étude VESPER ASCO 2023



- **Primary endpoint: PFS at 3 years**
- **median follow-up 40 months**

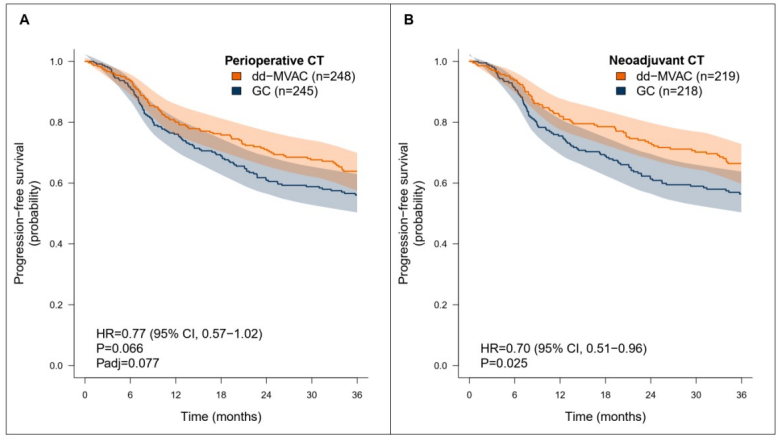
Neoadjuvant Subgroup	GC	DD-MVAC
Treatment Delivery of pre-planned cycles (%)	84	60
Radical Cystectomy performed (%)	90	91
Delay of Surgery (days)	48	51

	GC (N=245)	dd-MVAC (N=248)	P value
Nausea/vomiting	7 (2.9%)	24 (9.7%)	0.003
Diarrhea	2 (0.81%)	3 (1.2%)	-
Asthenia	10 (4.1%)	35 (14%)	<0.001
Cardiovascular	17 (6.9%)	16 (6.5%)	>0.9
Kidney	13 (5.3%)	15 (6.0%)	0.9
Liver	13 (5.3%)	7 (2.8%)	0.2
Neuropathy	0	2 (0.81%)	-
Anemia	19 (7.8%)	54 (22%)	<0.0001
Neutropenia	113 (46%)	97 (39%)	0.14
Febrile neutropenia	6 (2.4%)	16 (6.5%)	0.053
Thrombopenia	41 (17%)	49 (20%)	0.5
Chemotherapy-related deaths	1	3	-

Pfister Ch, et al. ESMO 2021; P6520; 2021 Feb;79(2):214-221; ContempClinTrials Commun. 2020; Grande E; invitedDiscussantP6520 ESMO2021

Péri-opératoire

Quel régime de chimiothérapie : étude VESPER



	GC	DD-MVAC
Patients enrolled	N=245	N=248
Peri-operative Chemotherapy		
Adjuvant (%)	11	12
Neoadjuvant (%)	89	88
NAC Subgroup		
Pathological Resonse (%)		
ypT0N0	36	42
ypTIS,Ta or T1 and ypN0	14	21
ypT2N0	13	14
≥ ypT3 or ypN+	37	22
Uncertain staiging	1	2
3yr PFS (%)	56	64

- MVAC dd> GC en PFS
- OS ?

Pfister Ch, et al. ESMO 2021; P6520; 2021 Feb;79(2):214-221; ContempClinTrials Commun. 2020; Grande E; invitedDiscussantP6520 ESMO2021

Péri-opératoire

Quel régime de chimiothérapie : étude VESPER

SG 5 ans : 64% MVAC dd vs 56% GC, HR, 0.77; 95% CI, 0.58-1.03; *p*=0.078),

Survie spécifique 72% vs 59%, HR, 0.63; 95% CI, 0.46-0.86; *p*=0.004)

En néoadjuvant : SG 66% vs 57%,HR, 0.71; 95% CI, 0.52-0.97; *p=0*.032)

Survie spécifique (75% vs 60%, HR, 0.56; 95% CI, 0.39-0.80; *P*=0.001

	GC	DD-MVAC
Patients enrolled	N=245	N=248
Peri-operative Chemotherapy		
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Neoadjuvant (%)	89	88
NAC Subgroup		
Pathological Resonse (%)		
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MVAC dd > Cisplatine gemcitabine

Pfister Ch, et al. ESMO 2021; P6520; 2021 Feb;79(2):214-221; ContempClinTrials Commun. 2020; Grande E; invitedDiscussantP6520 ESMO2021

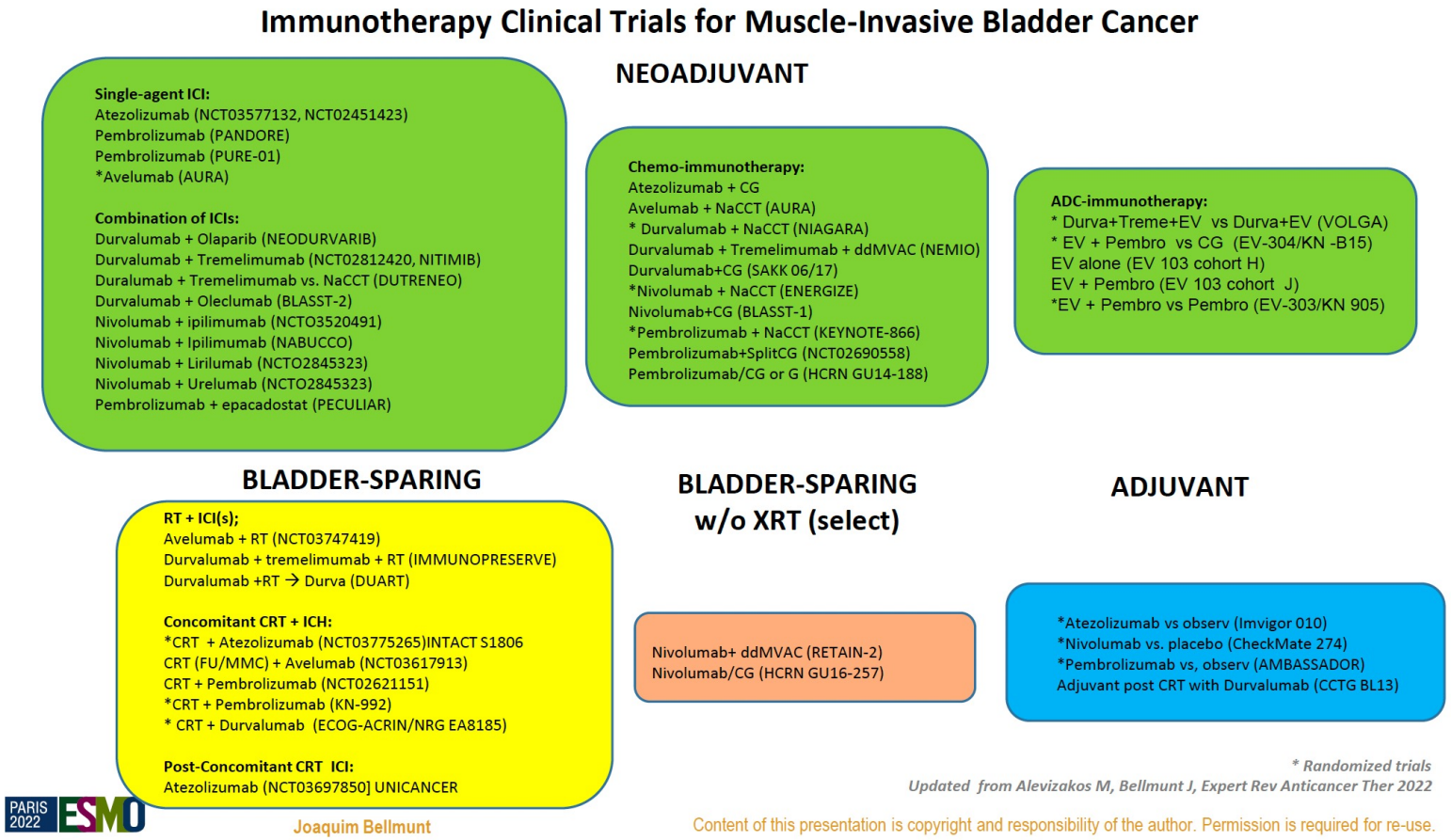
Péri-opératoire

Stratégie périopératoire

- MVAC dd > Cisplatine Gemcitabine
- Comment améliorer la pCR ?
- Et pour les non fit au Cisplatine ?

Péri-opératoire

Place de l'immunothérapie



** Randomized trials*

Updated from Alevizakos M, Bellmunt J, Expert Rev Anticancer Ther 2022

Péri-opératoire

Place de l'immunothérapie : immunothérapie seule en néoadjuvant

	PURE-01	ABACUS	MDACC	NABUCCO	DUTRENEO	BLASST-2
	Pembrolizumab	Atezolizumab	Durvalumab + Tremelimumab	Nivolumab + Ipilimumab	Durvalumab + Tremelimumab	Durvalumab
Sample size (N)	50	95	34	24	61	10
Population by cisplatin eligibility (Galsky criteria)	Eligible and ineligible	Ineligible or reject chemo	Cisplatin Ineligible	Ineligible or reject chemo	Eligible	Ineligible or reject chemo
PDL1+ (N,%)	35/30 (70)	39/95 (41)	NR	15/24 (63)	36/61 (59)	NR
Pathological Complete Responses (pCR) (%)	42	31	41	46	35	10
pCRs in PDL1+ (%)	54	37	NR	60	57	NR
pCRs in PDL1- (%)	13	24	NR	22	14	NR

- Pour rappel VESPER : PCR (ypT0N0)
  - MVAC dd :42 %
  - GC : 36 %

Necchi A, et al. JClinOncol2018, PowlesT, et al. NatMed2019, Gao J, et al. ASCO 2019, van derHeijdenMS, et al. ESMO 2019, WeiXX, et al. ASCO GU 2020, GuptaS, et al. ASCO GU 2020, Grande E, et al. ASCO 2020, HoimesCJ, et al. ASCO 2020, KaimakliotisHZ, et al. ASCO 2020

Péri-opératoire

Chimio-immunothérapie

Chemo-immunotherapy in patients with MIBCStudy	UNC LCCC1520	HCRN 14-188	BLASST-1	MSKCC	AURA	SAKK 06/17
# Patients	39	43	41	39	58	53
Immunotherapy	Pembrolizumab	Pembrolizumab	Nivolumab	Atezolizumab	Avelumab	Durvalumab
Chemotherapy	Gem/cis	Gem/cis	Gem/cis	Gem/cis	Gem/Cis	Gem/cis
pCR(pT0)	36%	44%	34%	38%	38%	34%
pRR(<pT2)	56%	61%	66%	69%	61%	60%

Rose et al, JCO 2021.
Hoimeset al, ESMO 2018, abstr5681.
Gupta et al, JCO 38,6_supp (Feb 2020).
Cathomas et al, ASCO 2022, abstr4515.
Funtet al, JCO, 2022.

Péri-opératoire

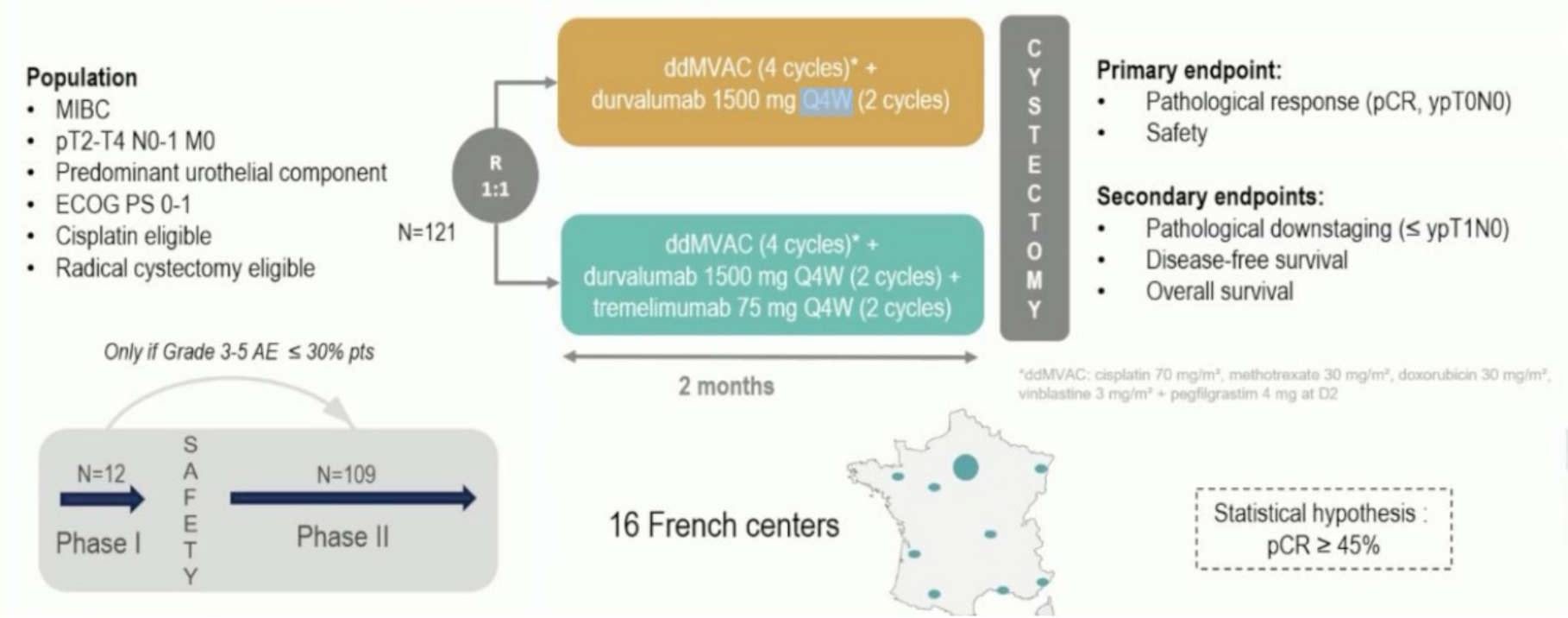
Chimio-immunothérapie : étude phase 3 en cours

Trial	n	Immunotherapy	Chemotherapy	Primary Outcome	Adjuvant?
NIAGARA	1050	Durvalumab	Gemcitabine + Cisplatin	Co: pCR + EFS	Yes – durva arm only
Keynote-866	790	Pembrolizumab	Gemcitabine + Cisplatin	Co: pCR + EFS	Yes – pembro arm only
ENERGIZE	976	Nivolumab *or* Nivolumab + IDO1-inhibitor linrodostat	Gemcitabine + Cisplatin	Co: pCR + EFS	Yes – nivo arms only

Matthew Milowsky, MD

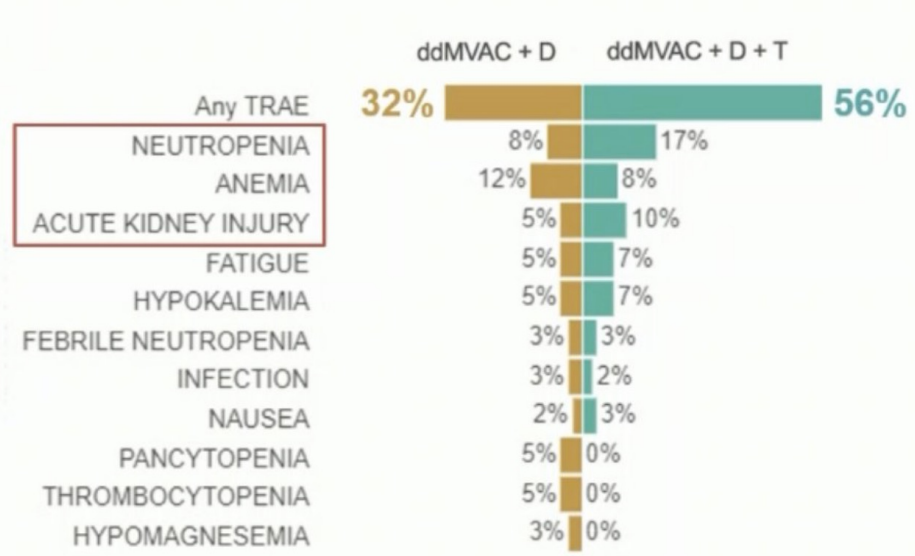
Péri-opératoire

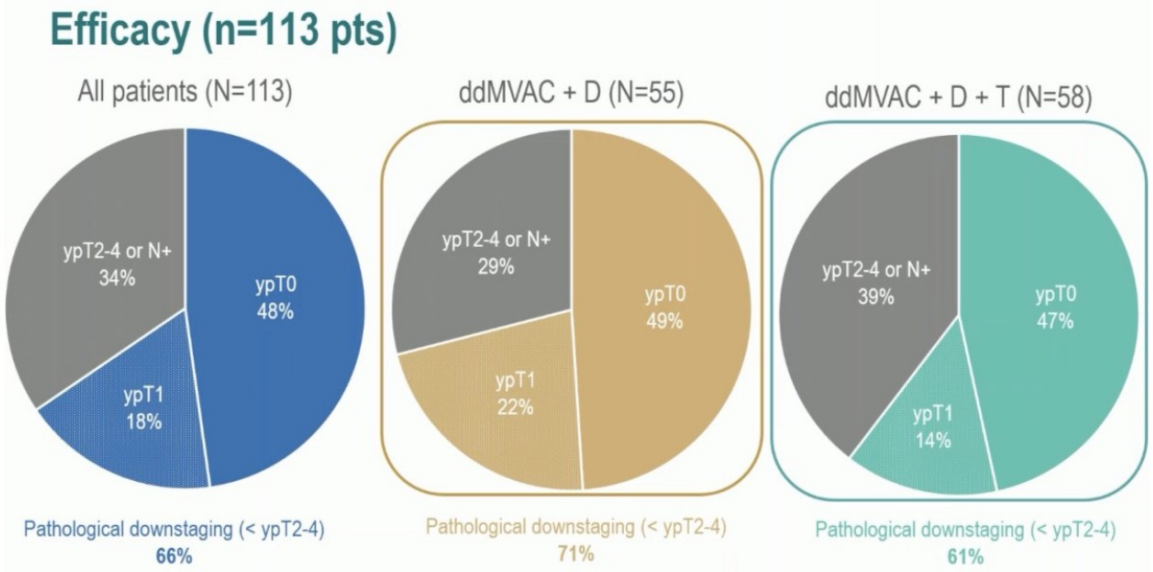
Chimio-immunothérapie : étude phase I/II NEMIO ESMO 2023



Péri-opératoire

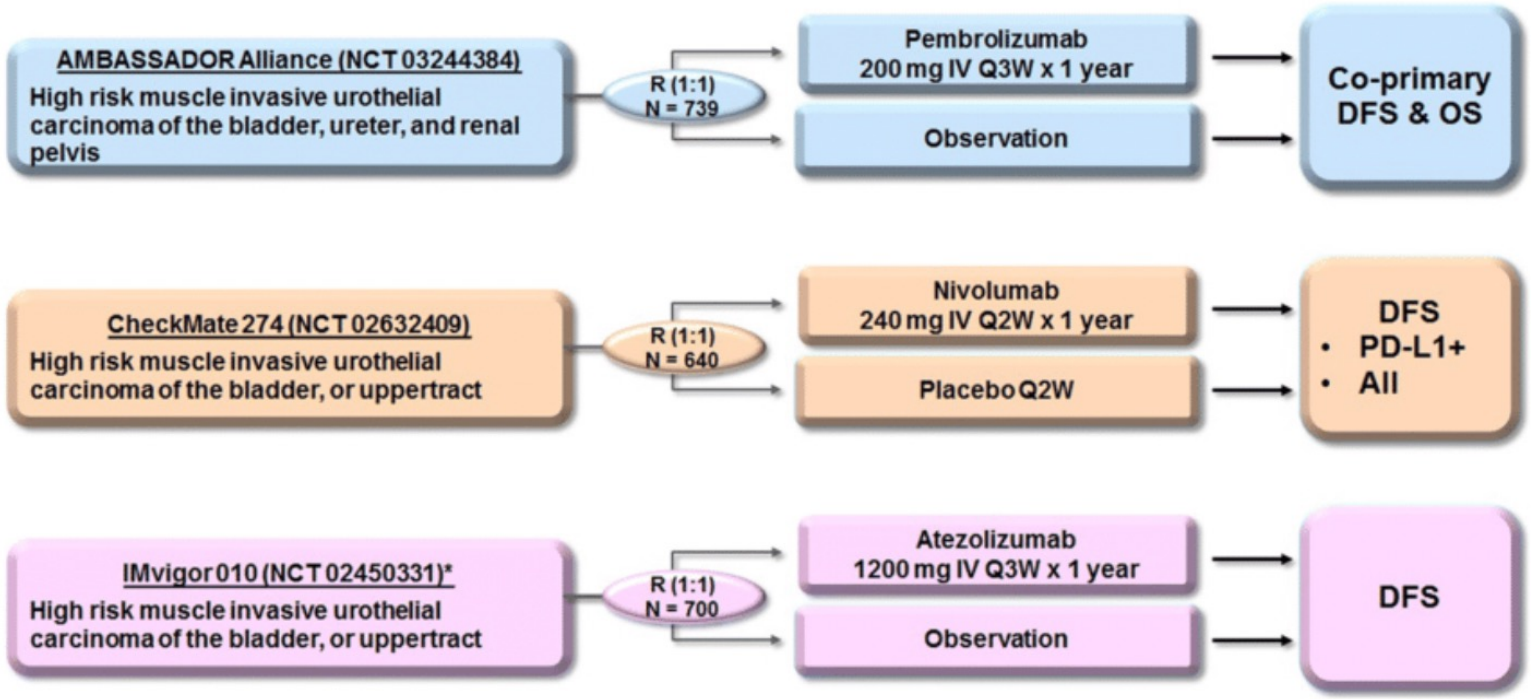
Chimio-immunothérapie : étude phase I/II NEMIO





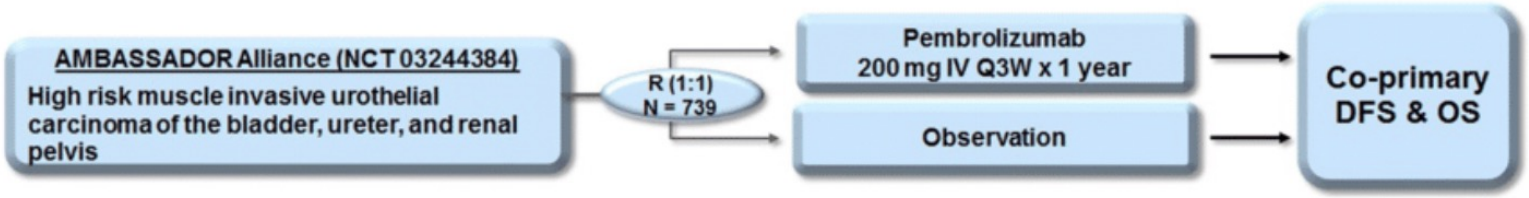
Péri-opératoire

Immunothérapie adjuvante :



Péri-opératoire

Immunothérapie adjuvante :



En cours…

Péri-opératoire

Immunothérapie adjuvante : mise à jour Checkmate 274 ASCO 2023

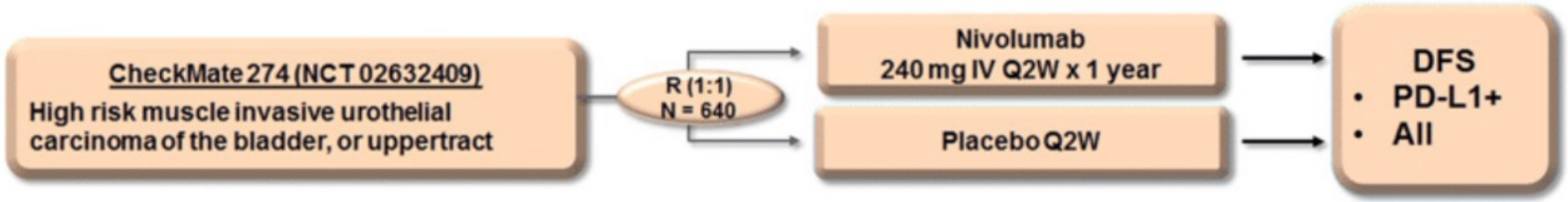
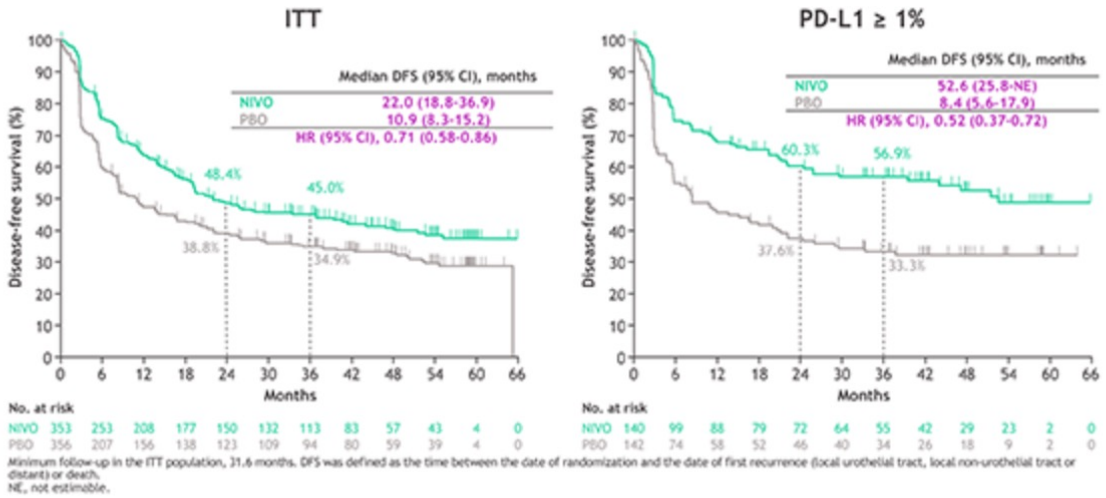


Figure 1. Disease-Free Survival (Primary Endpoint)



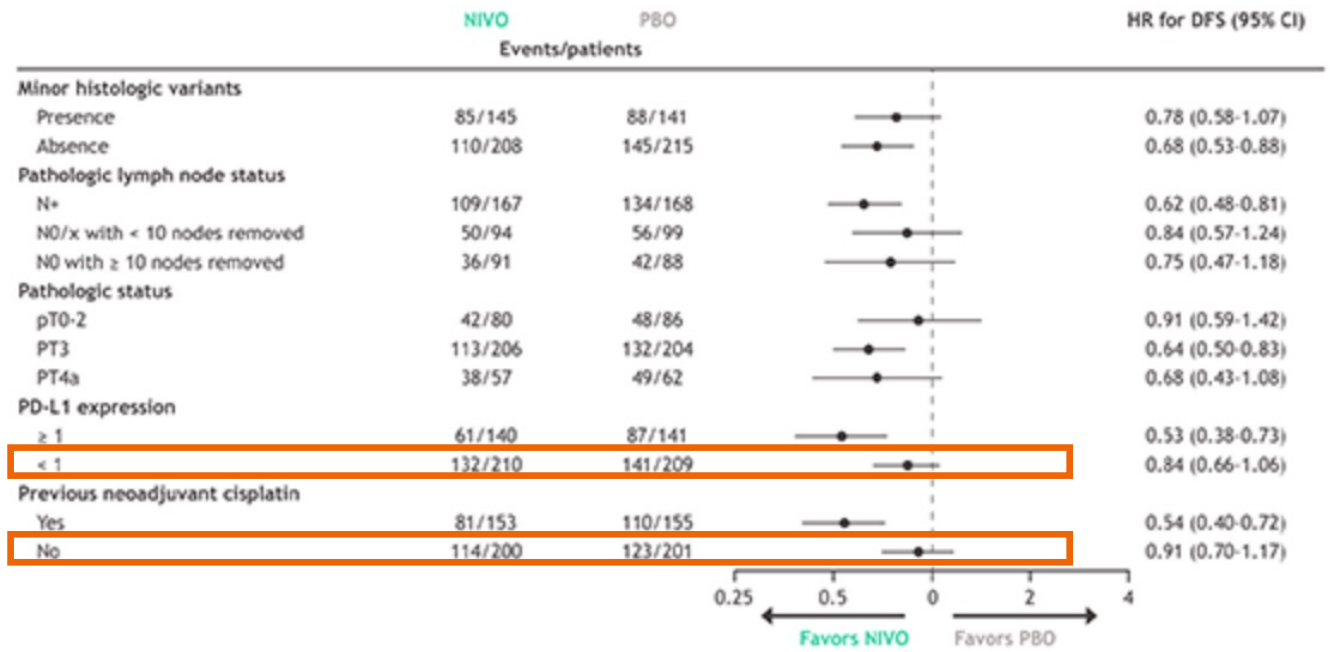
Abbreviations: DFS, disease-free survival; ITT, intention to treat; NE, not estimable; NIVO, nivolumab; PBO, placebo.View larger

- Confirmation bénéfice DFS : 20.8 mois vs 10.8 en ITT group (HR 0.70, 98.22% CI [0.55, 0.90]; *P* < .001)
- DFS non atteinte dans le groupe PDL1 + mais DFS à 6 mois à 74.5% vs 55.7% (HR 0.55, 98.72% CI [0.35, 0.85]; *P* < .001).

Péri-opératoire

Immunothérapie adjuvante : mise à jour Checkmate 274

Figure 3. DFS by Subgroup in the ITT Population: Histologic and Pathologic Data, PD-L1 Expression, and Cisplatin Status



Données OS en attente ++ surtout pour PDL1 – et naïf de chimiothérapie néoadjuvante

ACCES PRECOCE :

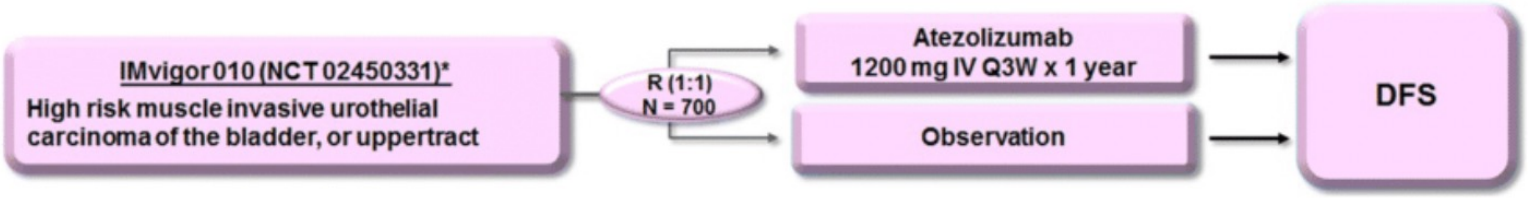
« En monothérapie dans le traitement adjuvant des patients adultes atteints de carcinome urothélial infiltrant le muscle (CUIM) à haut risque de récidive après exérèse complète, dont les cellules tumorales expriment PD-L1 au seuil ≥ 1% :

- **Patient(e) ayant reçu une chimiothérapie néoadjuvante : ypT2-ypT4a ou ypN+**
- **- Patient(e) n'ayant pas reçu de chimiothérapie néoadjuvante : pT3-pT4a ou pN+ et non éligible/ou ayant refusé une chimiothérapie adjuvante à base de cisplatine**

ASCO GU 2023 Galsky

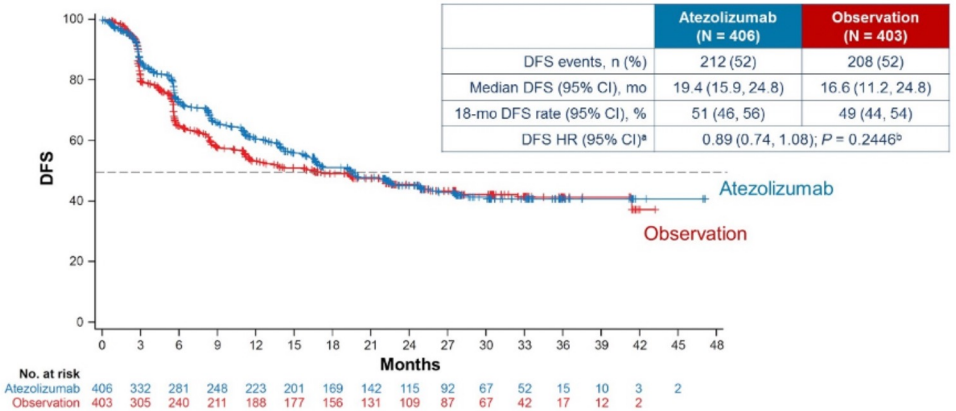
Péri-opératoire

Immunothérapie adjuvante :

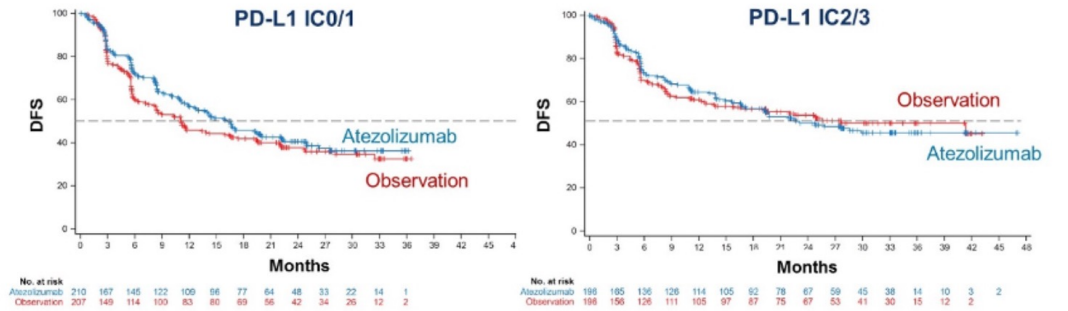


Median DFS : 19.4 months vs 16.6 months with observation, HR 0.89, P=0.2446.

DFS in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	



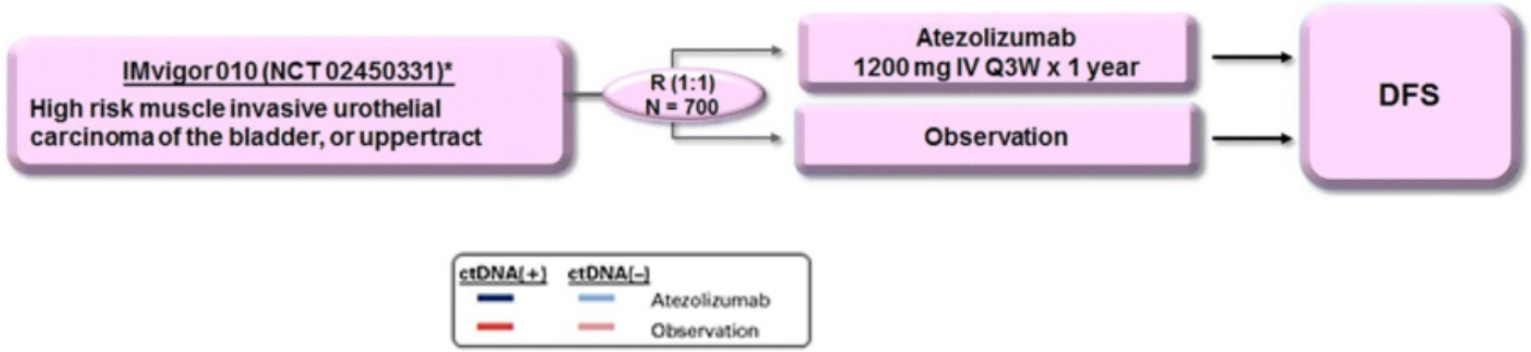
	Atezolizumab (n = 210)	Observation (n = 207)
DFS events, n (%)	118 (56)	120 (58)

Atezolizumab (n = 196)	Observation (n = 196)
94 (48)	88 (45)

ASCO 2021

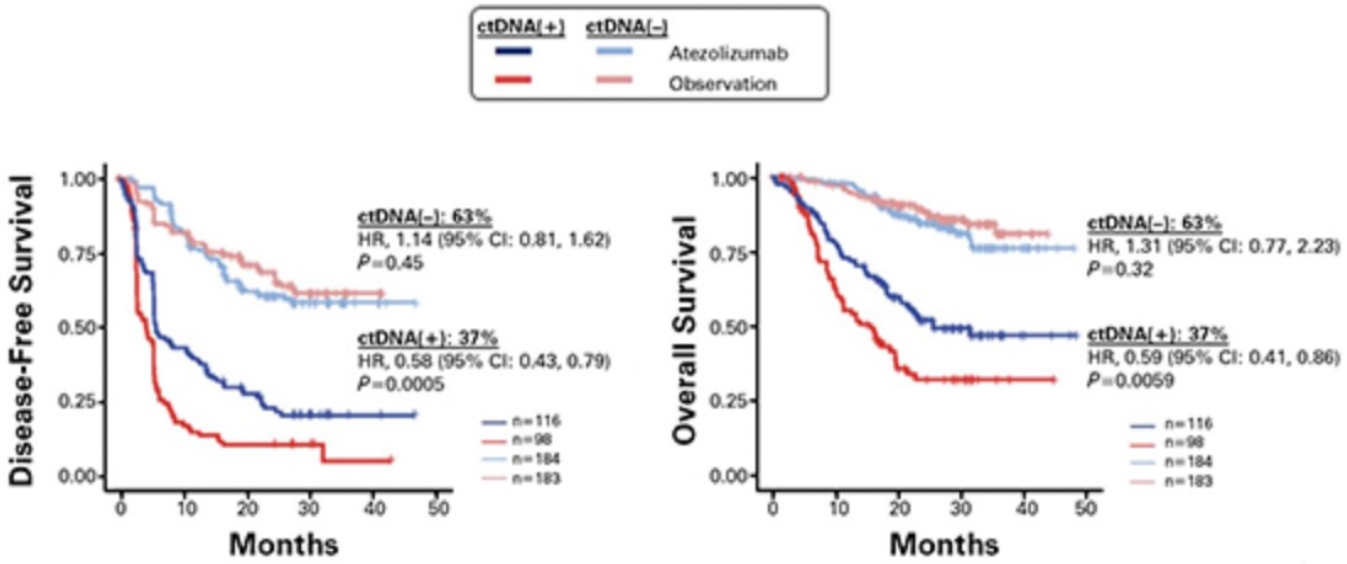
Péri-opératoire

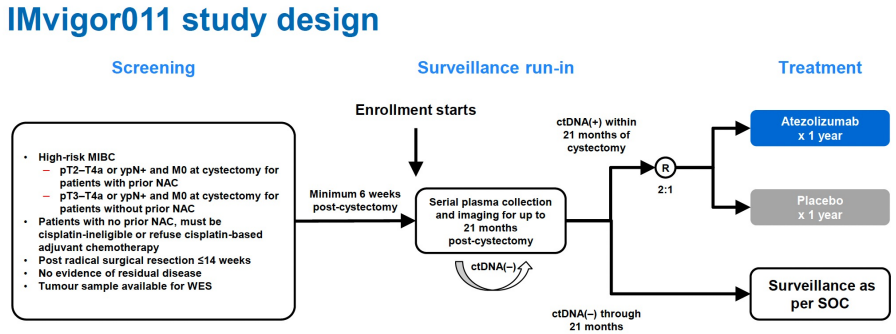
Immunothérapie adjuvante :



Intérêt de l'ADN circulant ?

En cours…

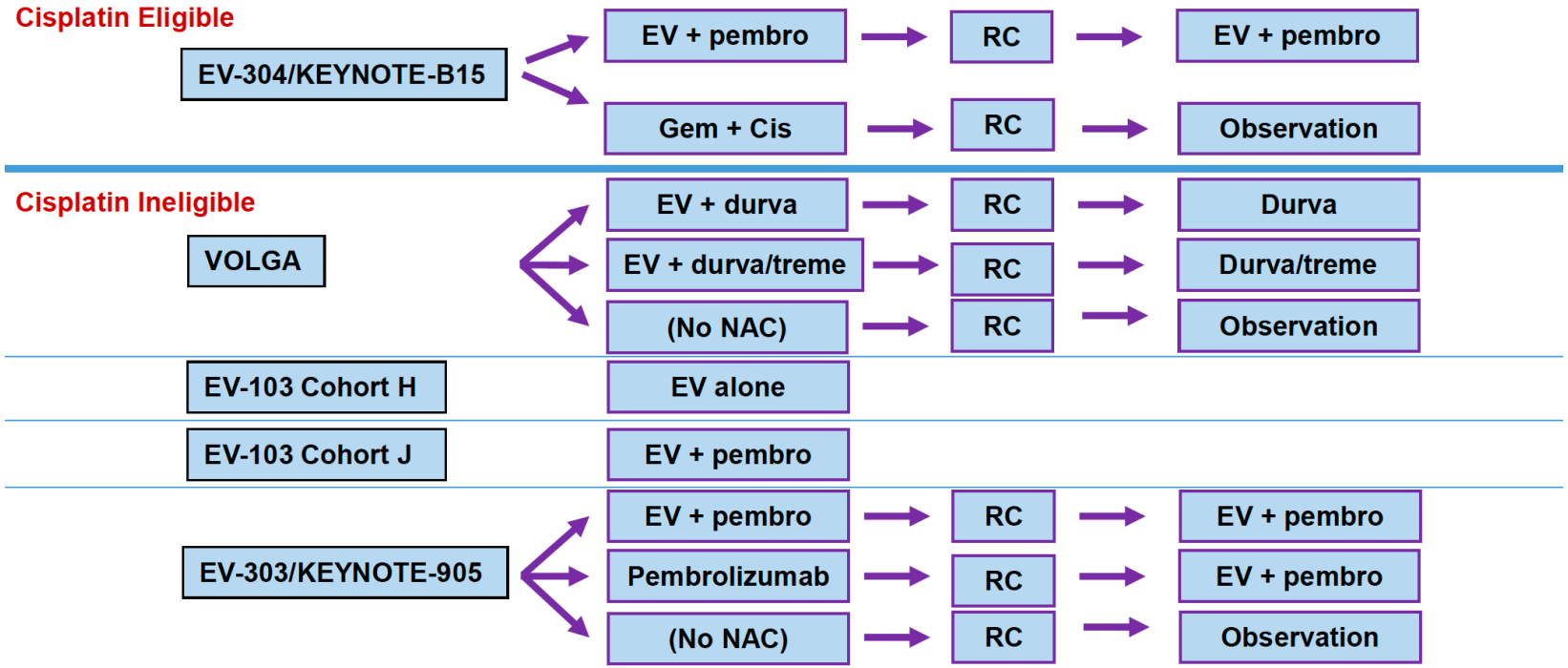




ASCO 2021

Péri-opératoire

ADC +/- IO : enfortumab vedotin ++



Adapté de M. Milowsky, ASCO 2022

Préservation de vessie

Recommandations AFU 2022-2024

Tableau de recommandation 3

Recommandations : Traitement des TVIM localisées	Grade
Faire une cystectomie, précédée d'une chimiothérapie néoadjuvante à base de cisplatine (traitement curatif de référence)	Fort
Faire la cystectomie par voie ouverte ou par voie coelioscopique simple ou robot-assistée	Fort
Faire un curage ganglionnaire pelvien étendu quelle que soit la voie d'abord au cours de la cystectomie	Fort
Favoriser la mise en place de protocoles de Récupération Améliorée Après Chirurgie	Fort
Demander une évaluation oncogériatrique en cas de TVIM chez un sujet de plus de 75 ans et/ou si score G8 ≤14.	Fort
Faire une évaluation de la fonction sexuelle chez l'homme et la femme et proposer une technique de préservation sexuelle et génitale chez les patients bien sélectionnés	Faible
Proposer un traitement conservateur trimodal associant RTUV complète, radiothérapie et chimiothérapie radio-sensibilisante en cas de tumeur de stade T2-T3, sans Cis, ni hydronéphrose.	Moyen

- Traitement conservateur trimodal en option
- Comment améliorer les stratégies de conservation d'organe ?

Préservation de vessie

RT +/- IO +/- CT

RT + ICI(s);
Avelumab + RT (NCT03747419)
Durvalumab + tremelimumab + RT (IMMUNOPRESERVE)
Durvalumab +RT → Durva (DUART)

Concomitant CRT + ICH:
*CRT + Atezolizumab (NCT03775265)INTACT S1806
CRT (FU/MMC) + Avelumab (NCT03617913)
CRT + Pembrolizumab (NCT02621151)
*CRT + Pembrolizumab (KN-992)
* CRT + Durvalumab (ECOG-ACRIN/NRG EA8185)

Post-Concomitant CRT ICI:
Atezolizumab (NCT03697850] UNICANCER

Préservation de vessie

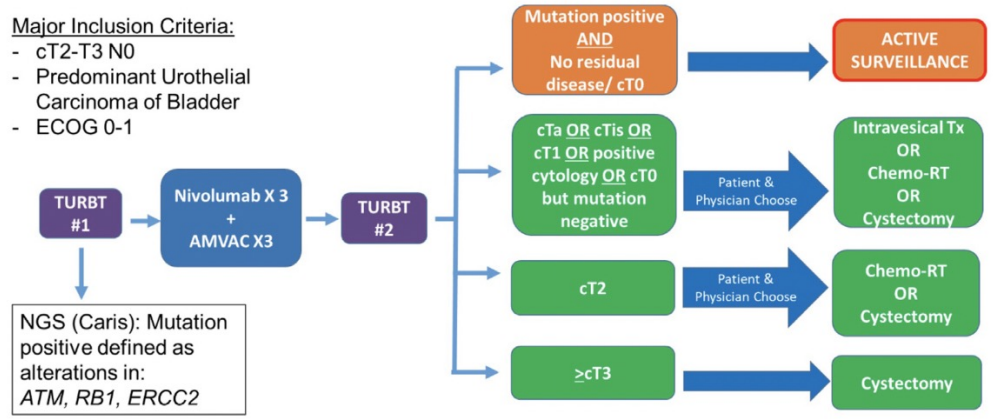
Traitement systémique seul

Nivolumab+ ddMVAC (RETAIN-2)
Nivolumab/CG (HCRN GU16-257)

Préservation de vessie

Traitement systémique seul

RETAIN-2

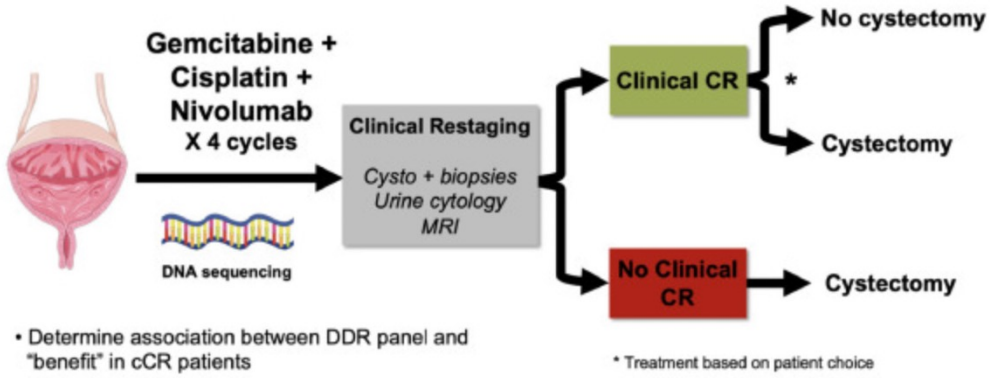


Metastasis-free survival (MFS) is defined as the absence of a recurrence of urothelial carcinoma that is >cN1 (more than one clinically suspicious pelvic lymph node) or surgically unresectable local recurrence (e.g., >cT4a) or M1 disease).

Primary endpt:
2-yr Metastasis-free survival
Follow-up: 5 years

Abbreviation: TURBT= transurethral resection of a bladder tumor, AMVAC=accelerated MVAC, NGS= next generation sequencing, chemo-RT= chemoradiation

HCRN GU16-257



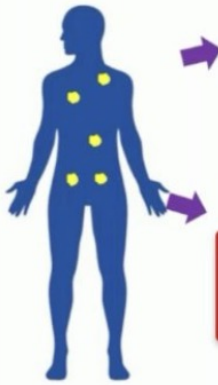
Abbreviation: DDR= DNA damage repair, CR= complete response, cCR= clinical complete response, MRI= magnetic resonance imaging

Cancer de vessie avancé

Cancer de vessie avancé

Standard of Care Management of Advanced/Metastatic Urothelial Carcinoma (pre-ESMO 2023)

First-Line



Cisplatin-eligible
- Cisplatin + gemcitabine[2]
- Dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (ddMVAC)[3]

Cisplatin-ineligible[1]
- Carboplatin + gemcitabine[4]
- *Enfortumab vedotin + Pembrolizumab[11] (accelerated approval)*

Platinum-ineligible
Pembrolizumab

Maintenance

For patients who achieve a response (CR/PR/SD) to platinum-based chemotherapy
- Avelumab[5]
- Pembrolizumab[6]

or Second-Line

- Pembrolizumab[7]
- Nivolumab
- Avelumab

Beyond-Second-Line

- Enfortumab Vedotin[8]
- Erdafitinib[9] (if tumor +FGFR 2/3 genetic alterations)
- Sacituzumab govitecan[10]
- Clinical trial
- Paclitaxel, docetaxel, or vinfluni

1. Galsky, et al. JCO 2011 Jun 10;29(17):2432-8
2. von der Maase, et al. JCO 2000 Sep 18;(17):3068-77
3.Sternerg, et al. JCO 2001 May 15;19(10):268-46
4. De Santis, et al. JCO 2012 Jan 10;30(2):191-9
5. Powles, et al., N Engl J Med 2020 Sep 24;383(13):1218-1230
6. Galsky et al., JCO. 2020 Jun 1;38(16):1797-1806.
7. Bellmunt et al., N Engl J Med 2017; 376:1015-1026
8. Powles T et al., N Engl J Med 2021;384:1125-35
9. Loriot Y, et al. N Engl J Med. 2019;381:338-348;
10. Tagawa CT et al., JCO 2021 Aug 1;39(22):2474-2485
11. O'Donnell PH et al., JCO. 2023 Sep 1;41(25):4107-4117

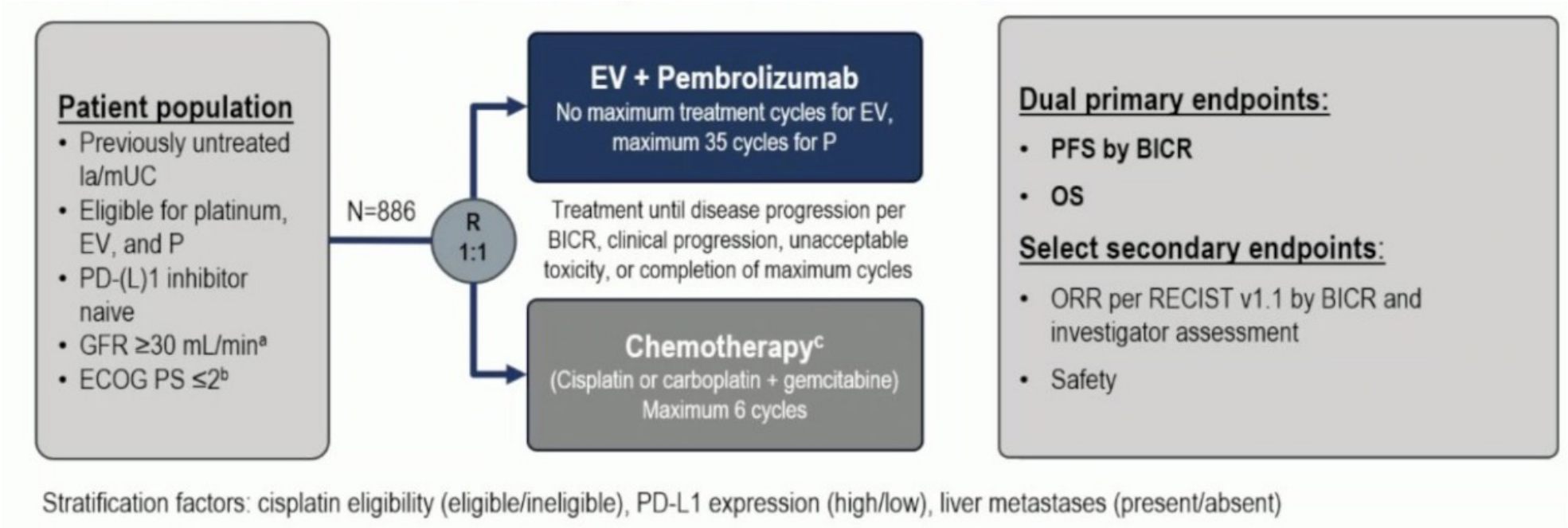
MADRID 2023 ESMO congress

Presented by Andrea B. Apolo, MD

@apolo_andrea

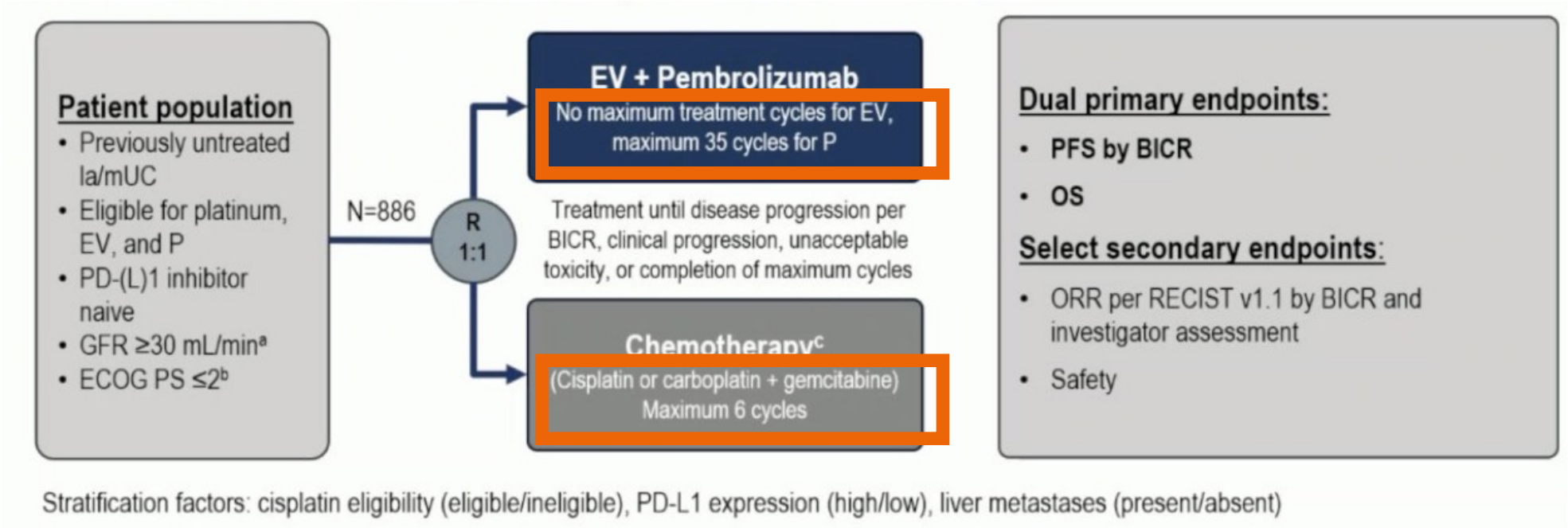
Première ligne métastatique

EV-302/KEYNOTE-A39 : EV + pembrolizumab vs chimiothérapie par platine ESMO 2023



Première ligne métastatique

EV-302/KEYNOTE-A39 : EV + pembrolizumab vs chimiothérapie par platine ESMO 2023



Première ligne métastatique

EV-302/KEYNOTE-A39 : EV + pembrolizumab vs chimiothérapie par platine ESMO 2023

	EV+P (N=442)	Chemotherapy (N=444)
Male sex, n (%)	344 (77.8)	336 (75.7)
Age (yrs), 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 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)

CPS, combined positive score

Première ligne métastatique

EV-302/KEYNOTE-A39 : EV + pembrolizumab vs chimiothérapie par platine ESMO 2023

	EV+P (N=442)	Chemotherapy (N=444)
Male sex, n (%)	344 (77.8)	336 (75.7)
Age (yrs), 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 World	167 (37.8)	162 (36.5)
ECOG PS, n (%)		
0	223 (50.5)	215 (48.4)
1	204 (46.2)	216 (48.6)
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Primary tumor location, n (%)		
Upper tract	135 (30.5)	104 (23.4)
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CPS, combined positive score

Première ligne métastatique

EV-302/KEYNOTE-A39 : EV + pembrolizumab vs chimiothérapie par platine ESMO 2023

	EV+P (N=442)	Chemotherapy (N=444)
Patients randomized, n (%)	442 (100)	444 (100)
Patients who received any amount of study drug, n (%)	440 (99.5)	433 (97.5)
Patients on treatment	144 (32.6)	0
Patients on study, n (%)	296 (67.0)	203 (45.7)
Primary reason for study treatment discontinuation[a], n (%)		
Completed treatment	8 (1.8)[b]	244 (55.0)
Progressive disease	153 (34.6)	73 (16.4)
Adverse event	97 (21.9)	62 (14.0)
Physician/Patient decision	31 (7.0)	52 (11.7)
Other[c]	7 (1.6)	2 (0.5)

Première ligne métastatique

EV-302/KEYNOTE-A39 : EV + pembrolizumab vs chimiothérapie par platine ESMO 2023

	EV+P (N=442)	Chemotherapy (N=444)
Patients randomized, n (%)	442 (100)	444 (100)
Patients who received any amount of study drug, n (%)	440 (99.5)	433 (97.5)
Patients on treatment	144 (32.6)	0
Patients on study, n (%)	296 (67.0)	203 (45.7)
Primary reason for study treatment discontinuation[a], n (%)		
Completed treatment	8 (1.8)[b]	244 (55.0)
Progressive disease	153 (34.6)	73 (16.4)
Adverse event	97 (21.9)	62 (14.0)
Physician/Patient decision	31 (7.0)	52 (11.7)
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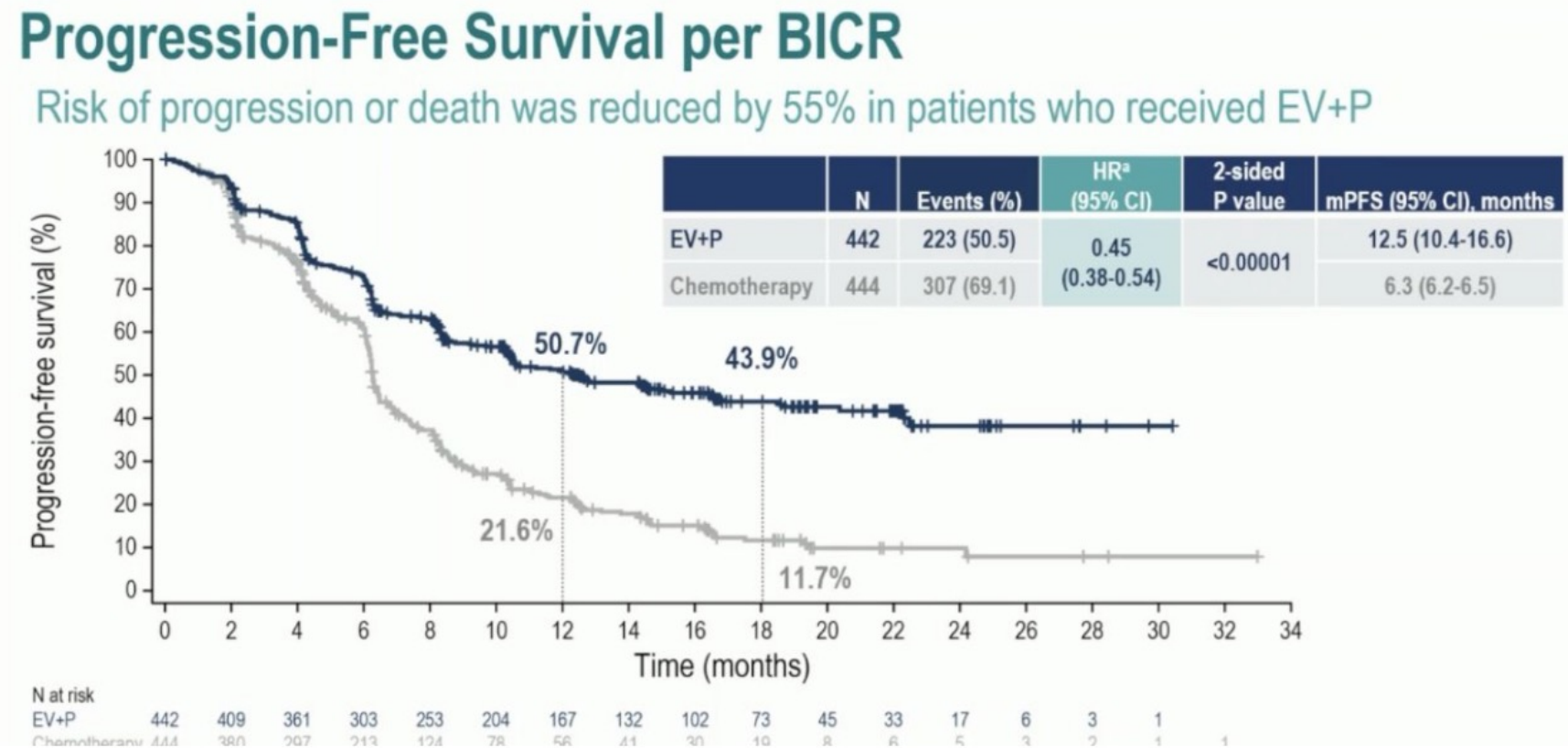
Première ligne métastatique

EV-302/KEYNOTE-A39 : EV + pembrolizumab vs chimiothérapie par platine ESMO 2023



	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)

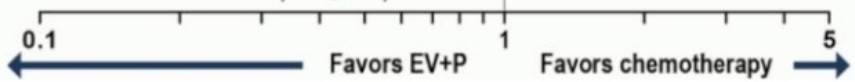
Première ligne métastatique

EV-302/KEYNOTE-A39 : EV + pembrolizumab vs chimiothérapie par platine ESMO 2023

Subgroup Analysis of PFS per BICR

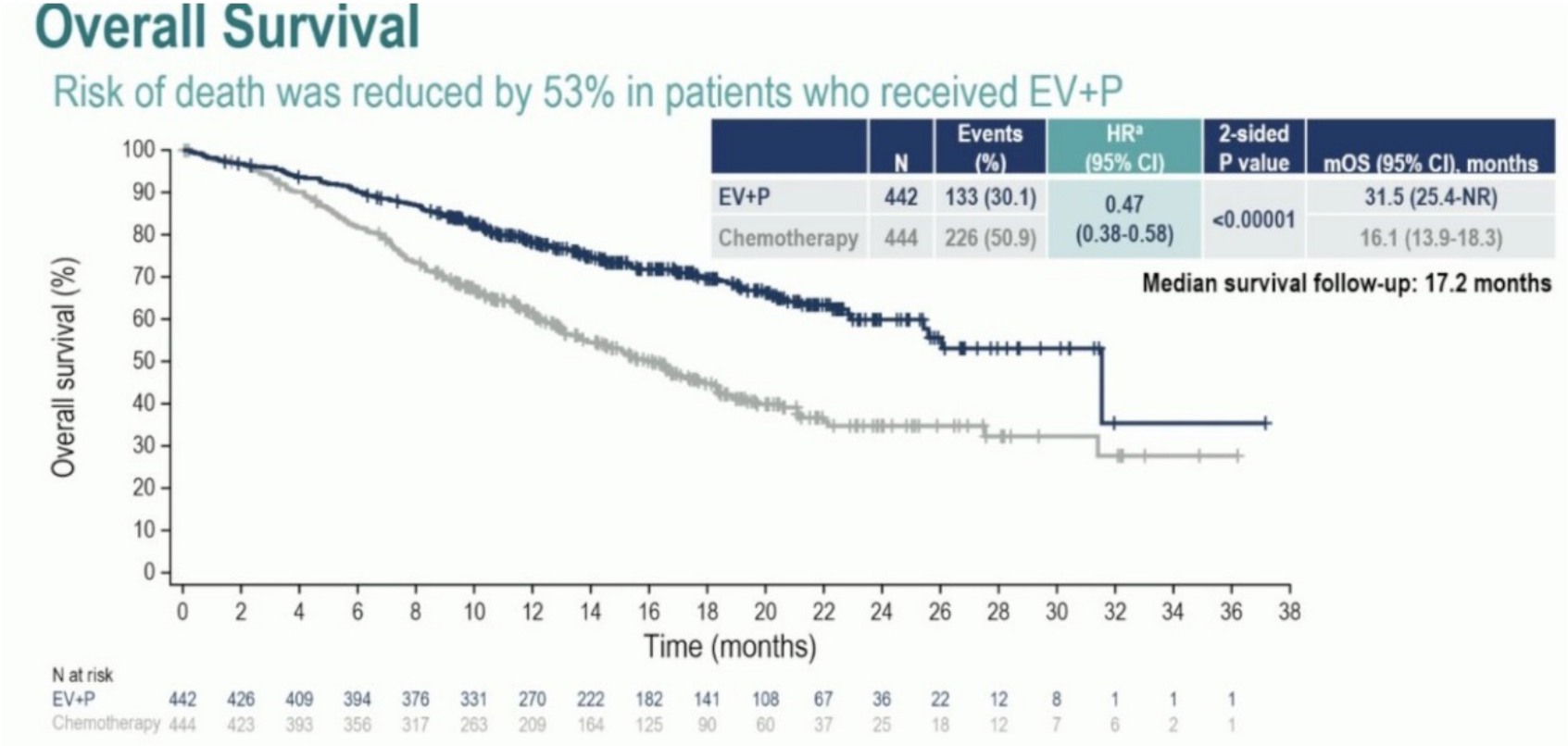
PFS benefit in select pre-specified subgroups was consistent with results in overall population

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	223/442	307/444	0.45 (0.38-0.54)
Age			
<65 years	75/144	88/135	0.45 (0.32-0.62)
≥65 years	148/298	219/309	0.45 (0.36-0.56)
Sex			
Female	55/98	74/108	0.49 (0.34-0.71)
Male	168/344	233/336	0.44 (0.36-0.54)
ECOG PS			
0	93/223	146/215	0.36 (0.28-0.48)
1-2	130/219	161/227	0.53 (0.42-0.68)
Primary disease site of origin			
Upper tract	69/135	70/104	0.50 (0.35-0.71)
Lower tract	152/305	236/339	0.44 (0.35-0.54)
Liver metastases			
Present	66/100	78/99	0.53 (0.38-0.76)
Absent	157/342	229/345	0.43 (0.35-0.52)
PD-L1 expression			
Low (CPS <10)	105/184	127/185	0.50 (0.38-0.65)
High (CPS ≥10)	116/254	176/254	0.42 (0.33-0.53)
Cisplatin eligibility			
Eligible	117/244	149/234	0.48 (0.38-0.62)
Ineligible	106/198	158/210	0.43 (0.33-0.55)



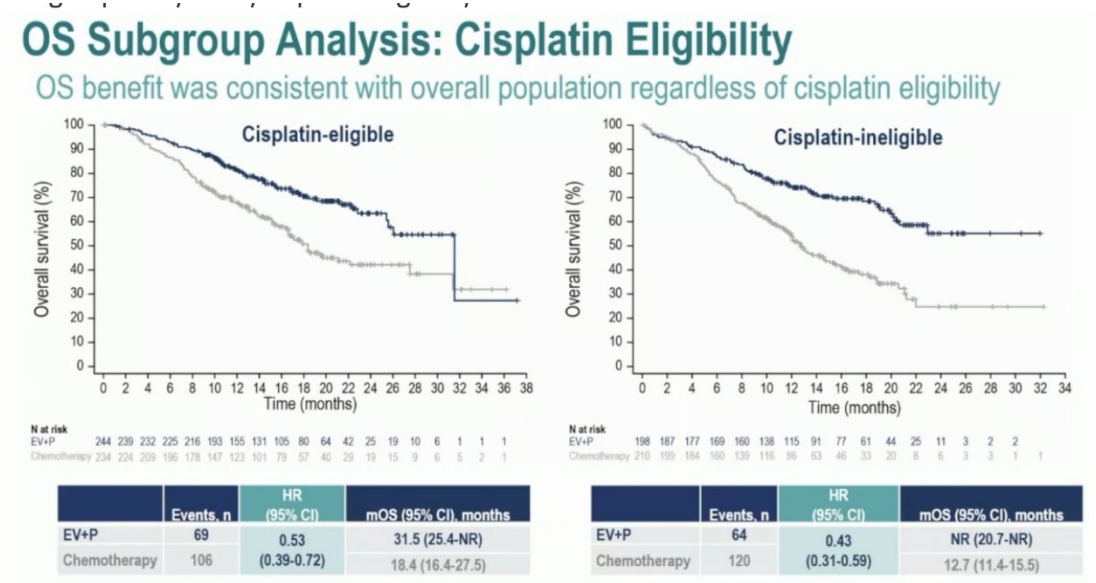
Première ligne métastatique

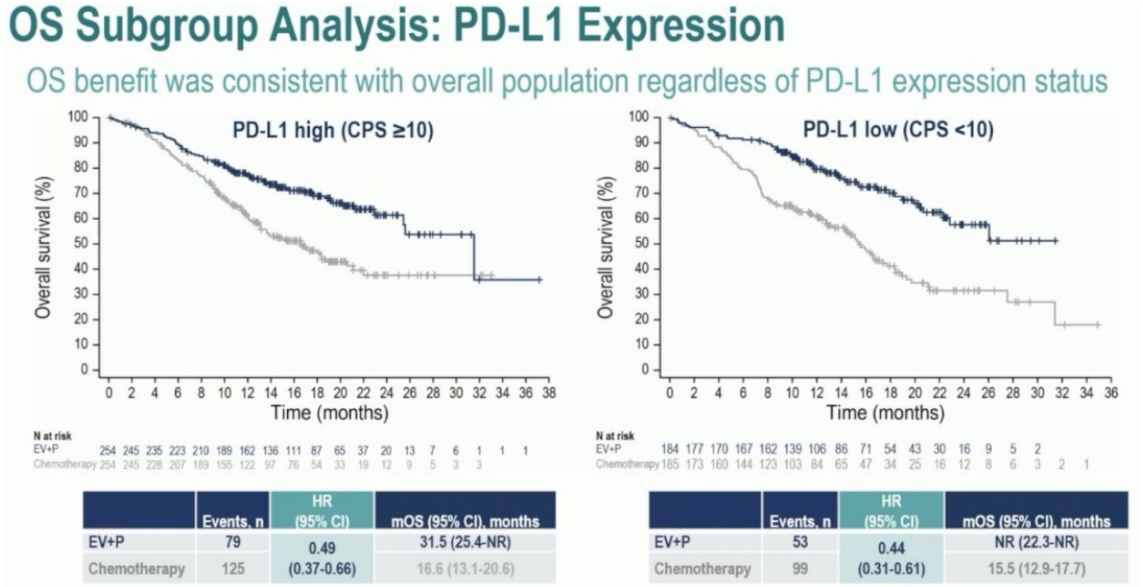
EV-302/KEYNOTE-A39 : EV + pembrolizumab vs chimiothérapie par platine ESMO 2023



Première ligne métastatique

EV-302/KEYNOTE-A39 : EV + pembrolizumab vs chimiothérapie par platine ESMO 2023



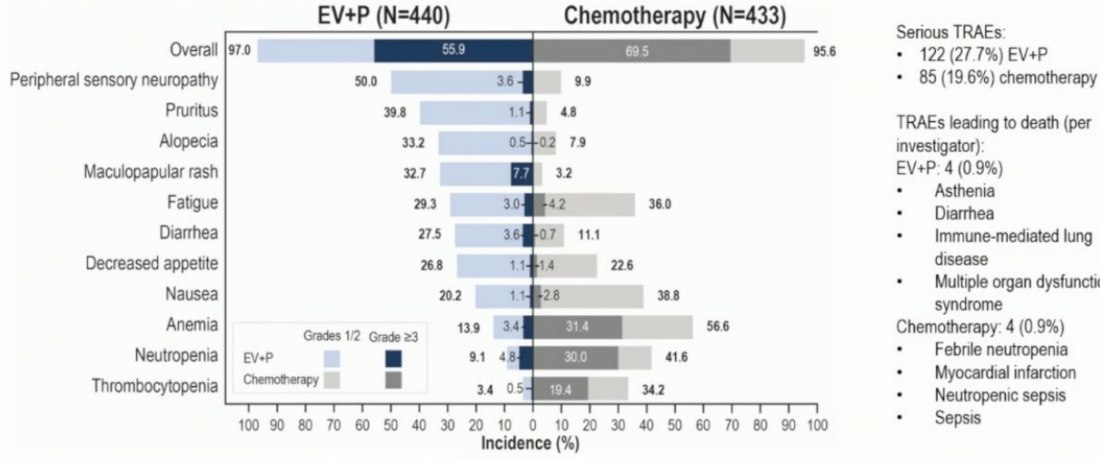


Première ligne métastatique

EV-302/KEYNOTE-A39 : EV + pembrolizumab vs chimiothérapie par platine ESMO 2023

Treatment-Related Adverse Events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy



Serious TRAEs:
- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):
EV+P: 4 (0.9%)
- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunctio syndrome

Chemotherapy: 4 (0.9%)
- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

EV Treatment-Related Adverse Events of Special Interest*

Majority of treatment-related AESIs were low grade

	EV+P (N=440) n (%)		Chemotherapy (N=433) n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Skin reactions	294 (66.8)	68 (15.5)	60 (13.9)	1 (0.2)
Peripheral neuropathy	278 (63.2)	30 (6.8)	53 (12.2)	0 (0.0)
Sensory events	260 (59.1)	19 (4.3)	51 (11.8)	0 (0.0)
Motor events	44 (10.0)	12 (2.7)	5 (1.2)	0 (0.0)
Ocular disorders	94 (21.4)	0 (0.0)	12 (2.8)	0 (0.0)
Dry eye	82 (18.6)	0 (0.0)	8 (1.8)	0 (0.0)
Hyperglycemia	57 (13.0)	27 (6.1)	3 (0.7)	0 (0.0)
Infusion-related reactions	9 (2.0)	0 (0.0)	9 (2.1)	0 (0.0)

Première ligne métastatique

EV-302/KEYNOTE-A39 : EV + pembrolizumab vs chimiothérapie par platine ESMO 2023

	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

Première ligne métastatique

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Other	11 (2.5)	17 (3.8)

[a]144 (32.6%) patients in the EV+P arm remain on treatment at time of analysis

- Seulement 30% d'avelumab en entretien dans le bras chimiothérapie
- Place de l'EV en 3ème L dans le bras chimiothérapie

Première ligne métastatique

EV-302/KEYNOTE-A39 : EV + pembrolizumab vs chimiothérapie par platine ESMO 2023

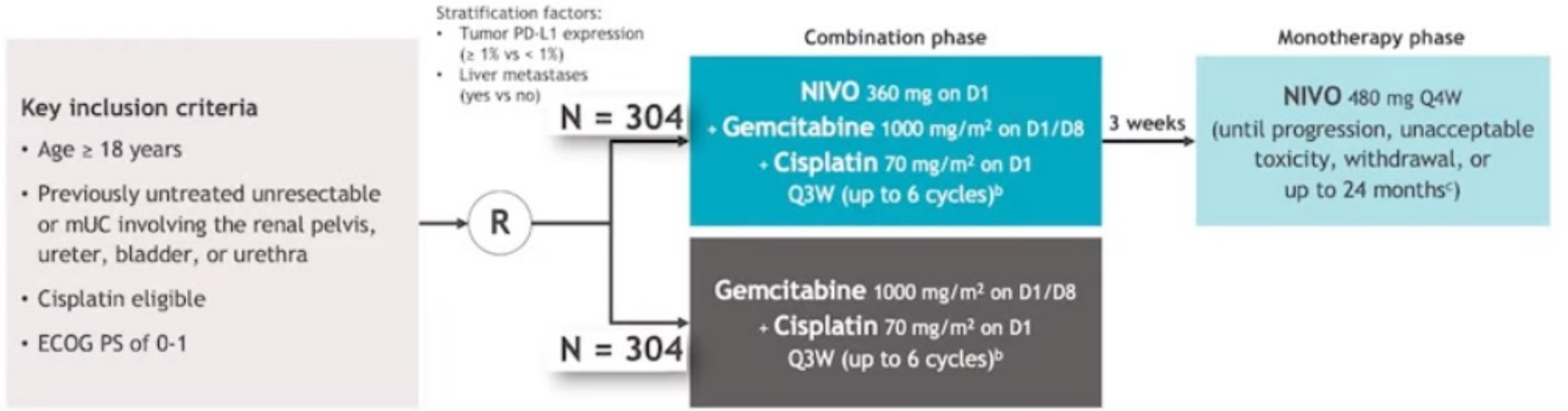
- Première fois que la chimiothérapie par platine est dépassée en 1ère ligne du cancer urothélial M+
- Doublement de la PFS et de l'OS
- Fit ou unfit cisplatine, PDL1 + ou -

- A confirmer : quid de la tolérance des patients hors essai, traitement poursuivi tant que efficace, seulement 32 % avelumab en entretien ?

Première ligne métastatique

Checkmate 901: chimiothérapie par cisplatine +/- nivolumab phase 3 ESMO 2023

- NIVO + gemcitabine-cisplatin vs gemcitabine-cisplatin in cisplatin-eligible patients[a]

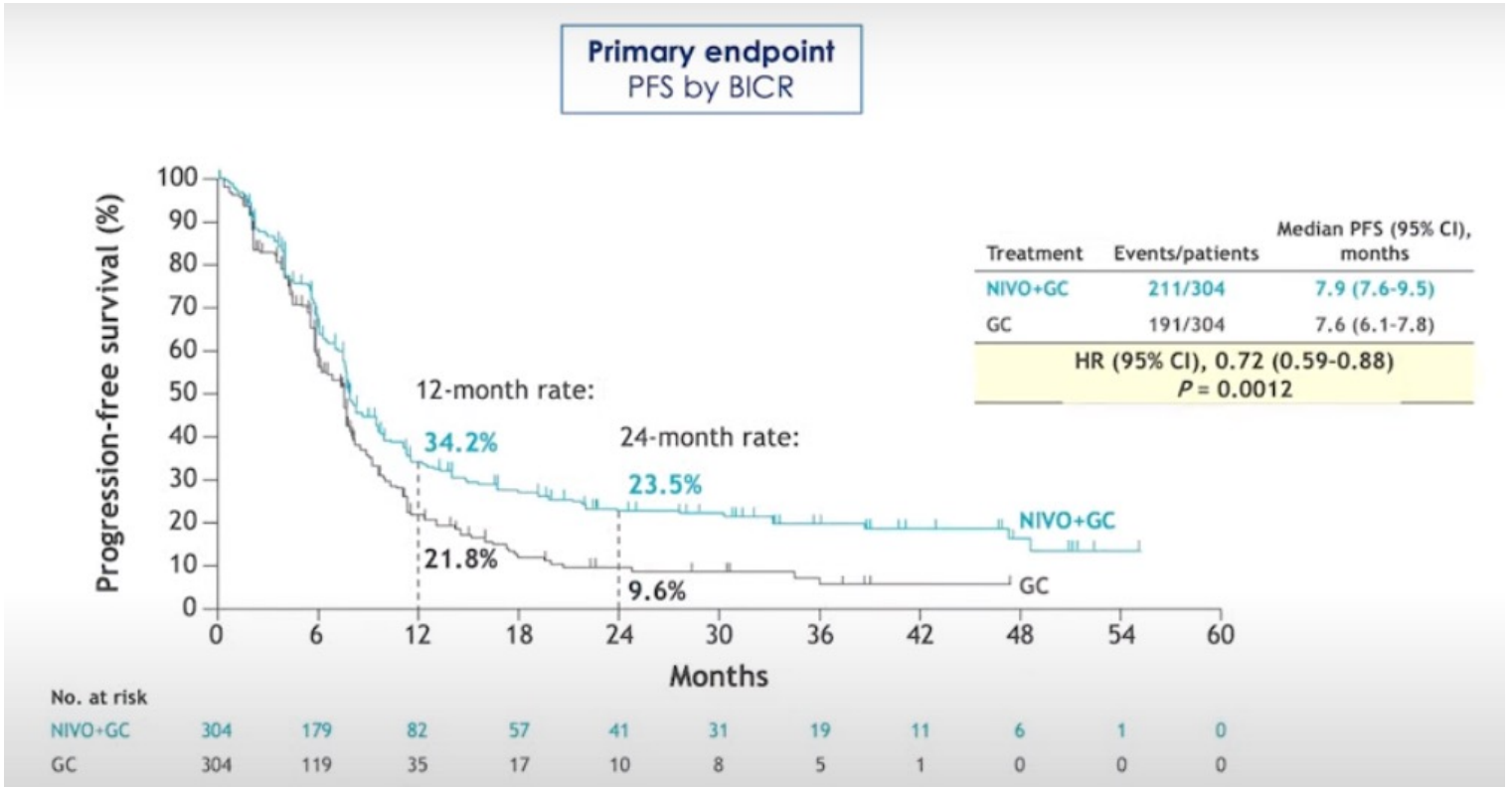


Median (range) study follow-up, 33.6 (7.4-62.4) months

Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS by PD-L1 ≥ 1%,[d] HRQoL
Key exploratory endpoints: ORR per BICR, safety

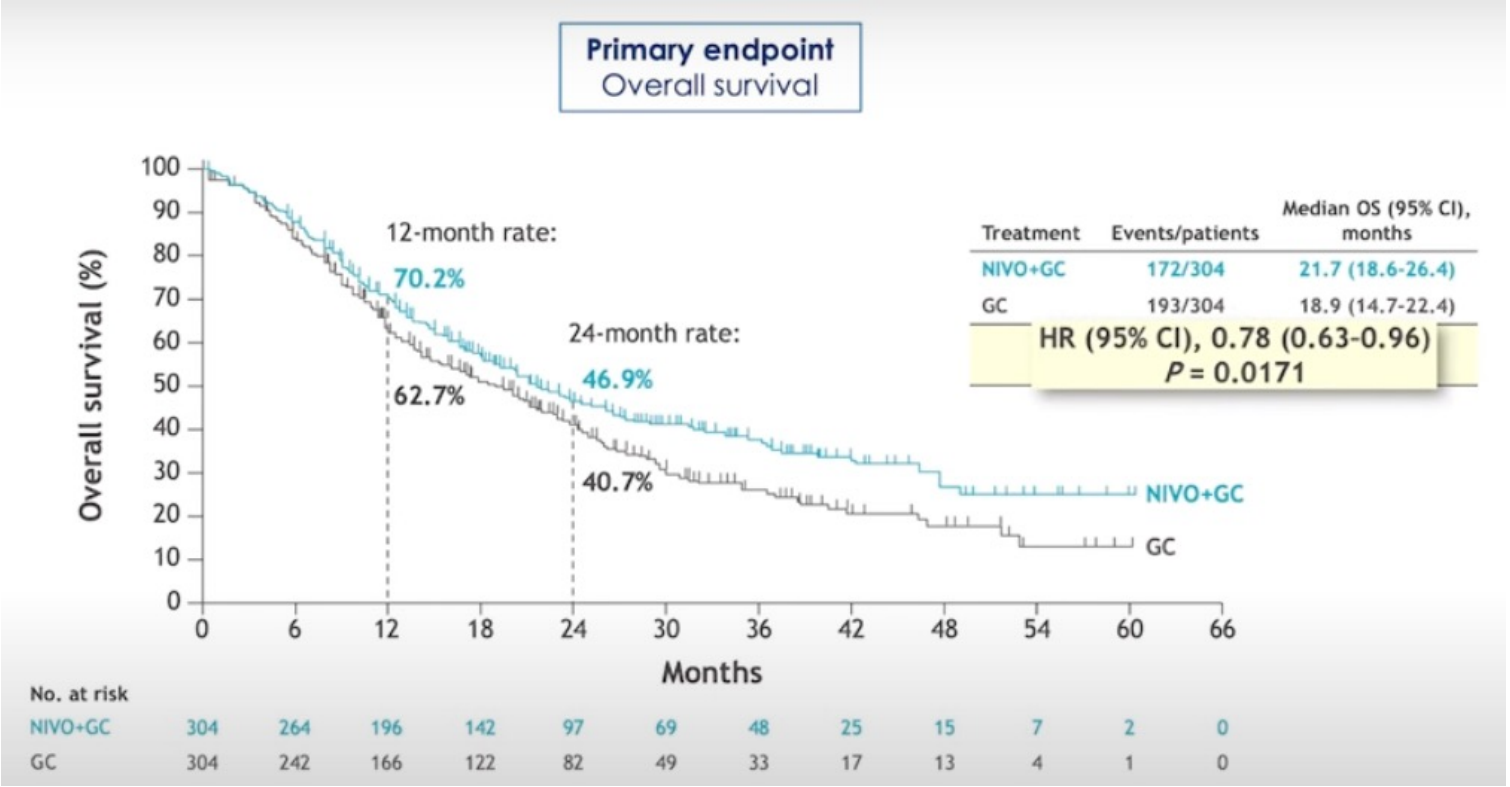
Première ligne métastatique

Checkmate 901: chimiothérapie par platine +/- nivolumab phase 3 ESMO 2023



Première ligne métastatique

Checkmate 901: chimiothérapie par platine +/- nivolumab phase 3 ESMO 2023

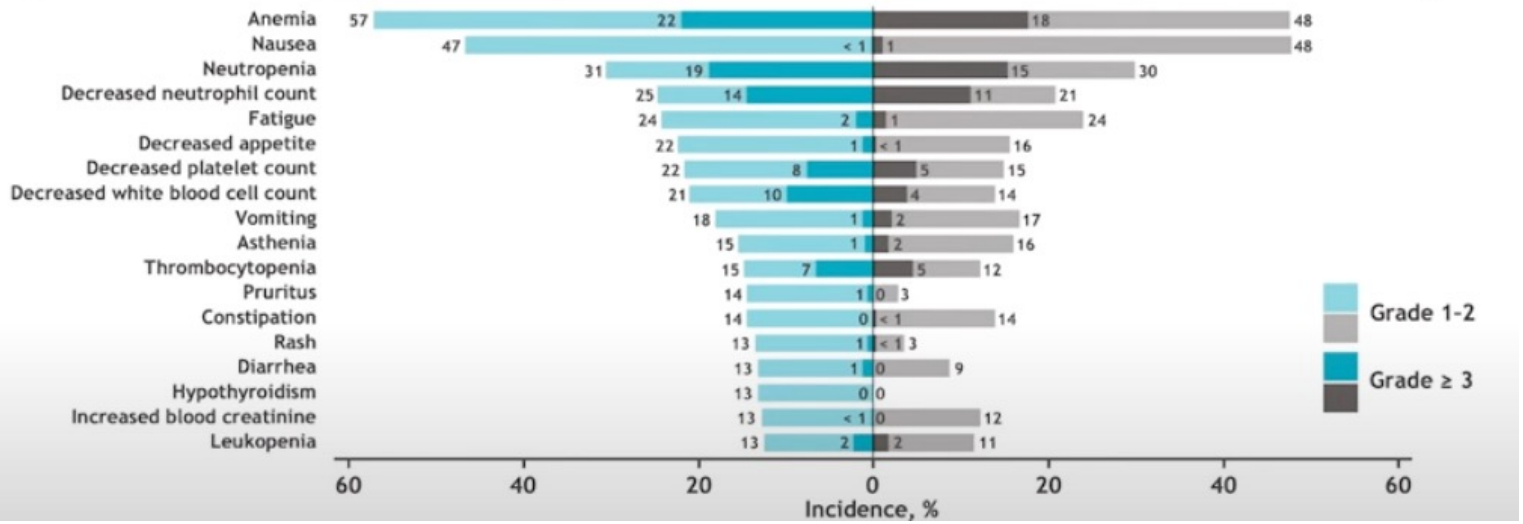


Première ligne métastatique

Checkmate 901: chimiothérapie par platine +/- nivolumab phase 3 ESMO 2023

Treatment-related AEs in all treated patients

	NIVO+GC (n = 304)		GC (n = 288)	
Treatment-related AE, %[a]	Any grade	Grade ≥ 3[b]	Any grade	Grade ≥ 3[b]
Any	97	62	93	52
Leading to discontinuation	21	11	17	8



Première ligne métastatique

Checkmate 901: chimiothérapie par platine +/- nivolumab phase 3 ESMO 2023

- Deuxième essai où la chimiothérapie par platine est dépassée en 1ère L du carcinome urothélial M+
- Intérêt de l'association Chimio + IO vs chimio + maintenance IO ?
- Arrivée un peu trop tard ? Comment choisir ?

Première ligne métastatique

Checkmate 901: chimiothérapie par platine +/- nivolumab phase 3 ESMO 2023

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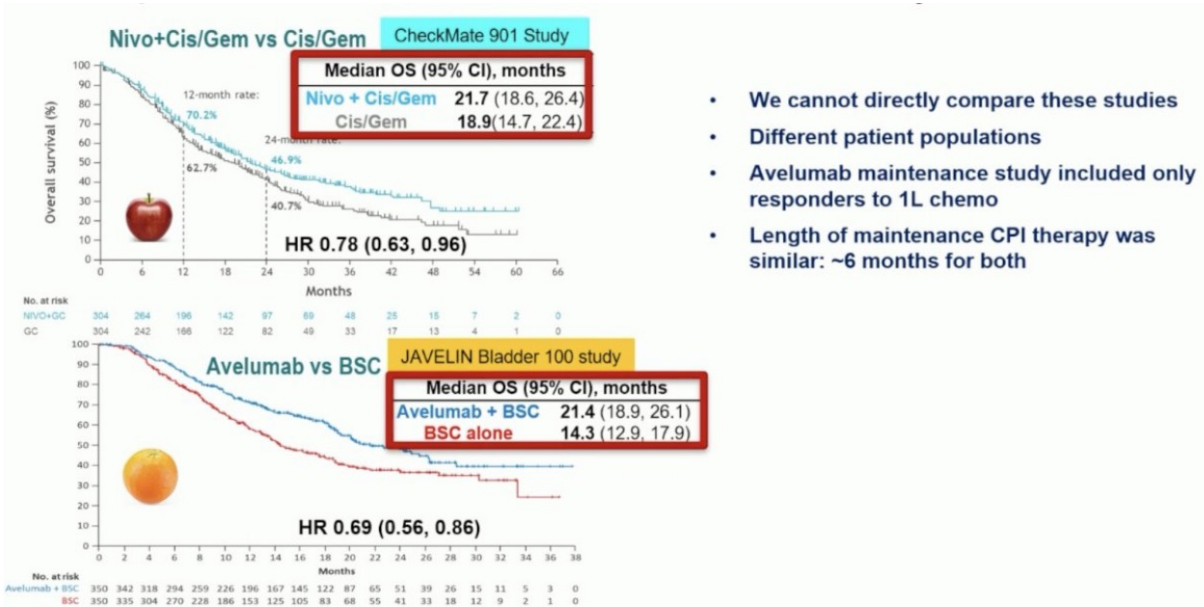
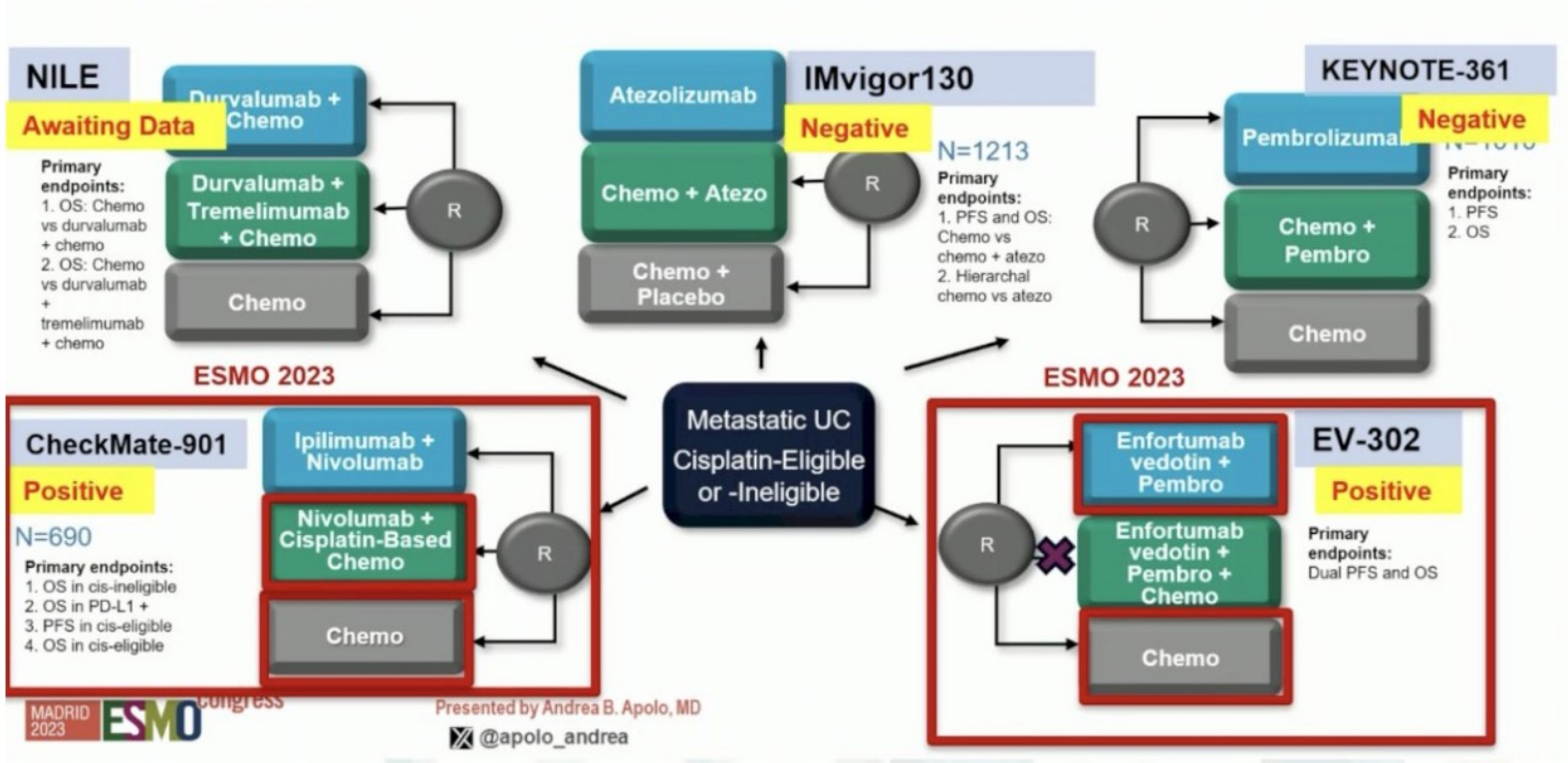
- Intérêt de l'association Chimio + IO vs chimio + maintenance IO ?



- We cannot directly compare these studies
- Different patient populations
- Avelumab maintenance study included only responders to 1L chemo
- Length of maintenance CPI therapy was similar: ~6 months for both

Première ligne métastatique

Comment choisir ?

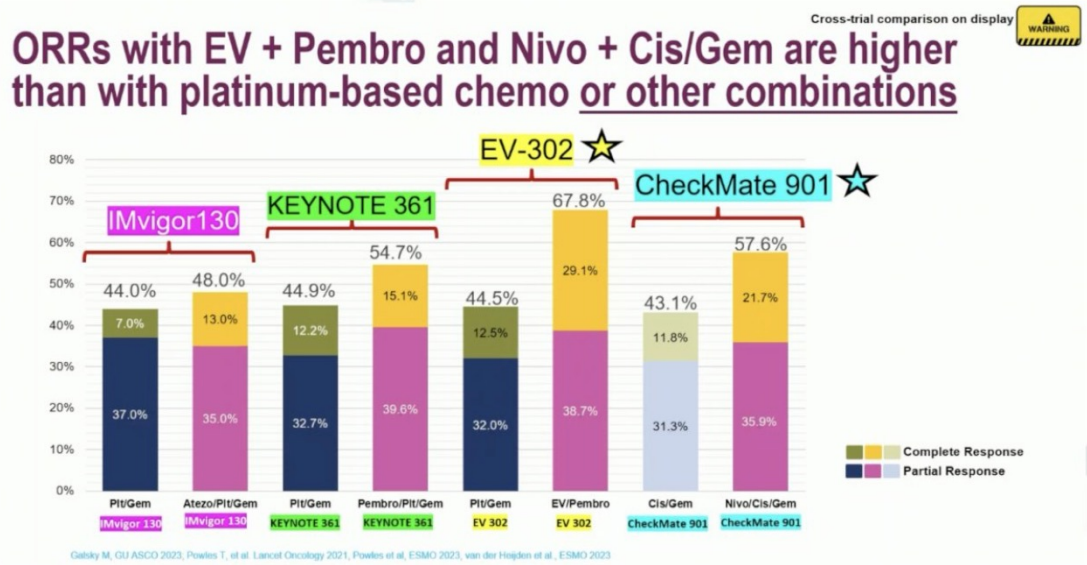


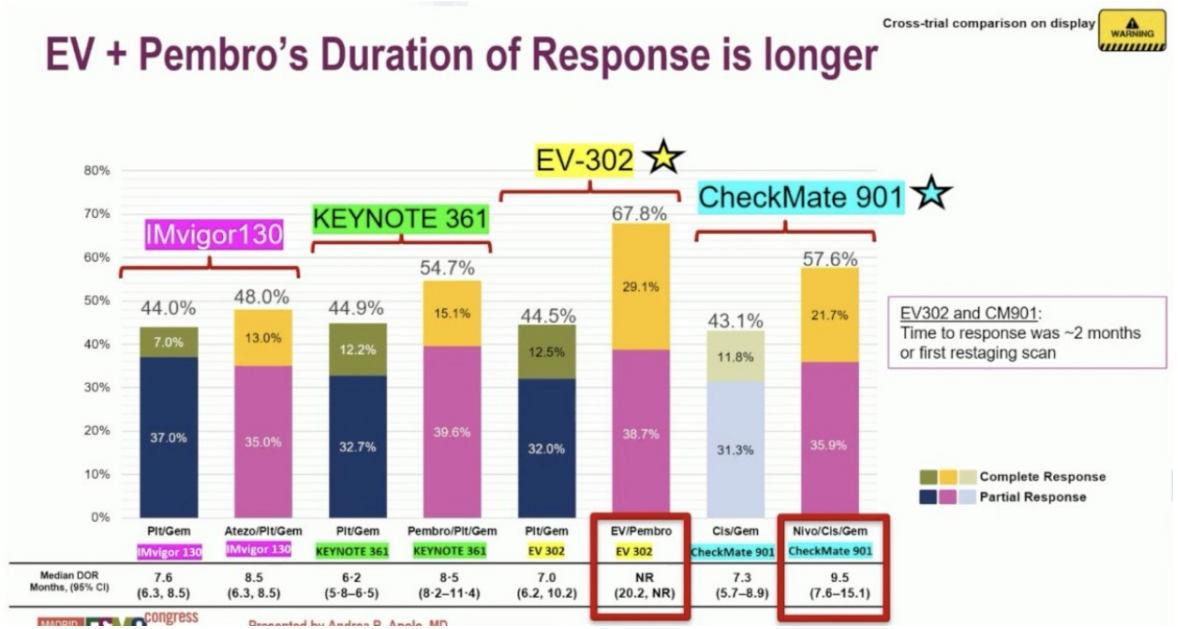
Première ligne métastatique

Comment choisir ? Taux de réponse, durée de réponse, toxicité, survie globale

Première ligne métastatique

Comment choisir ? Taux de réponse, durée de réponse, toxicité, survie globale





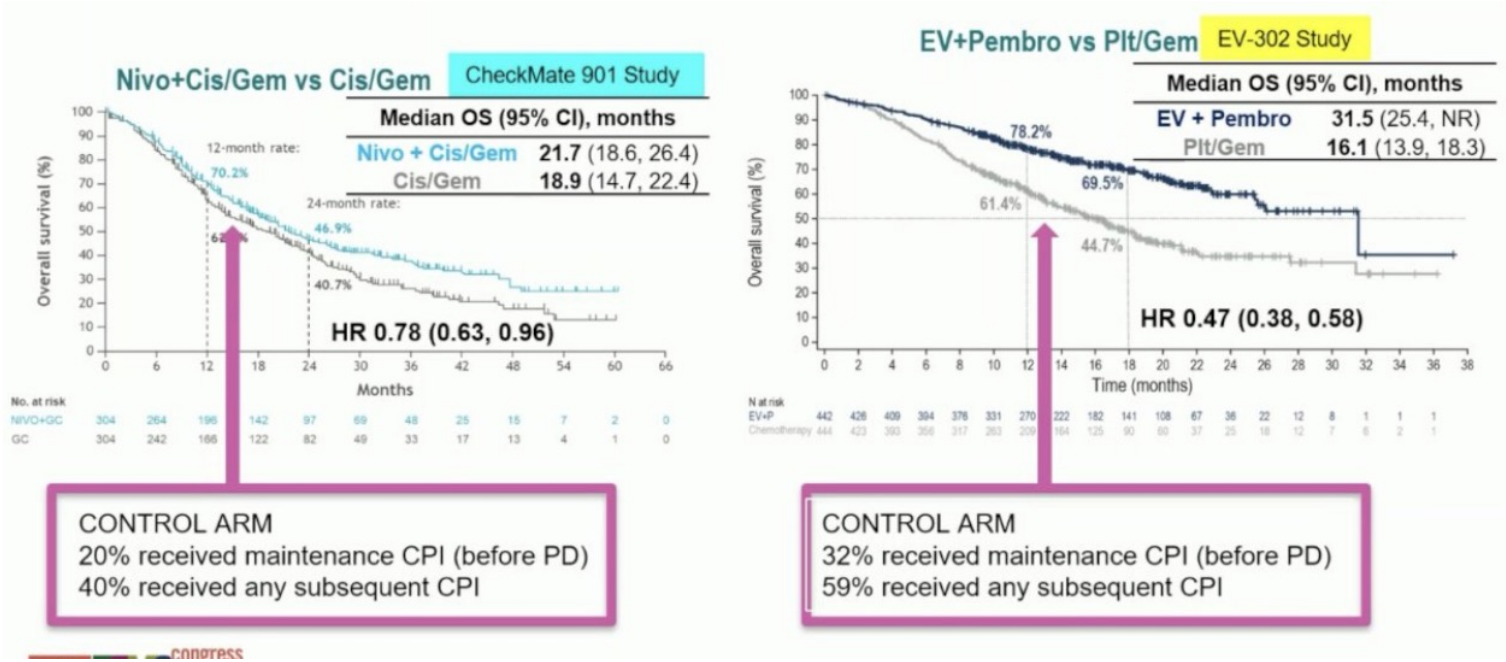
Première ligne métastatique

Comment choisir ? Taux de réponse, durée de réponse, toxicité, survie globale

- Toxicité grade 3 : 56% EV + P vs 62 % CHIMIO + N
- Profil de toxicité très différent
- Possibilité d'alléger la toxicité de l'EV ?

Première ligne métastatique

Comment choisir ? Taux de réponse, durée de réponse, toxicité, survie globale



- OS à 31,5 mois pour EV +P vs 21,7 mois pour chimio + N

Première ligne métastatique

Futur standard ?

First-Line

- Enfortumab vedotin + Pembrolizumab

Second-Line?

Cisplatin-eligible

- Cisplatin + gemcitabine
- Dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (ddMVAC)

Cisplatin-ineligible

- Carboplatin + gemcitabine

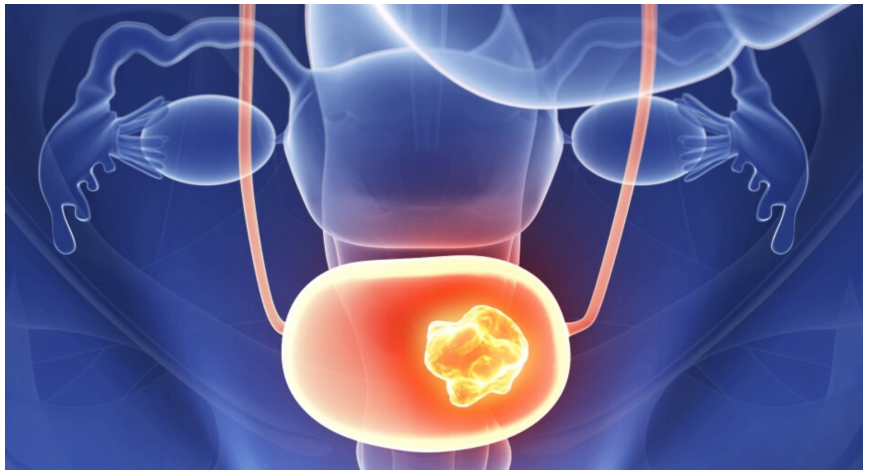
Beyond-Second -Line

- Erdafitinib (if tumor + FGFR 2/3 genetic alterations)
- Sacituzumab govitecan
- Clinical trial
- Paclitaxel, docetaxel, or vinflunine

A. Apolo ESMO 2023

Métastatique : nouvelles drogues

FGFR



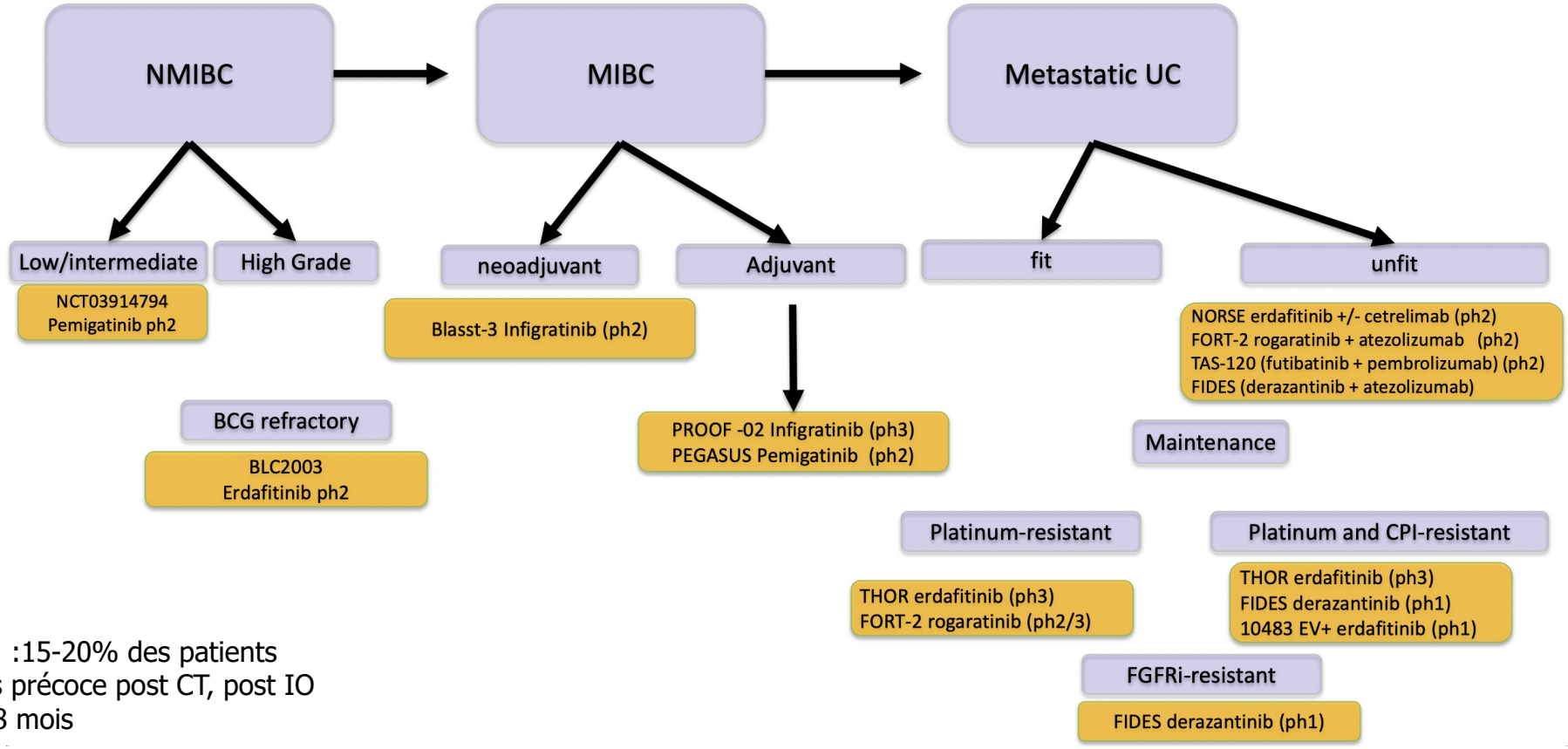
Réparation ADN

Protéines de membranes

Angiogénèse

Métastatique : nouvelles drogues

FGFR

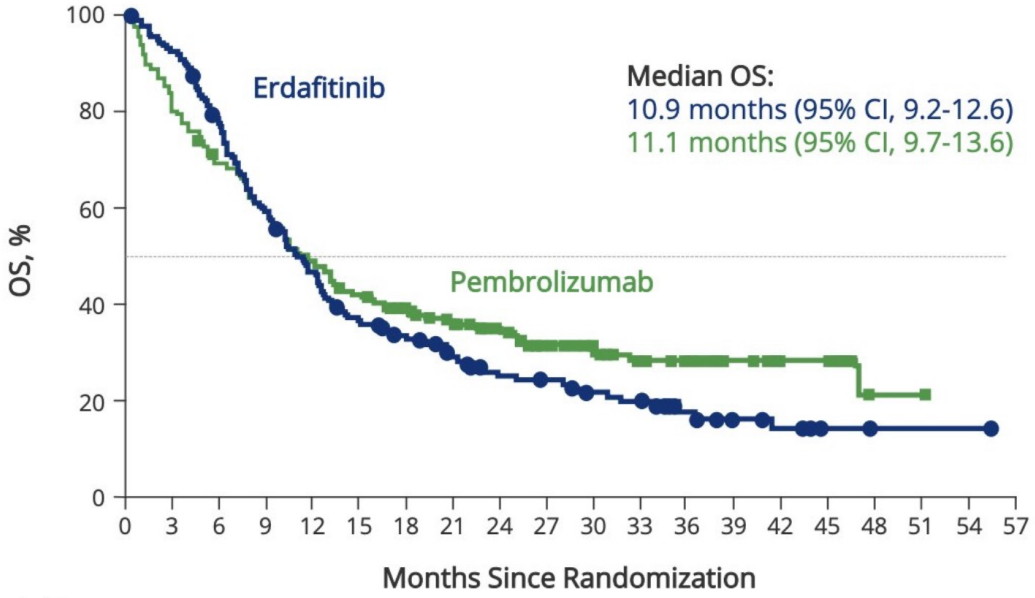


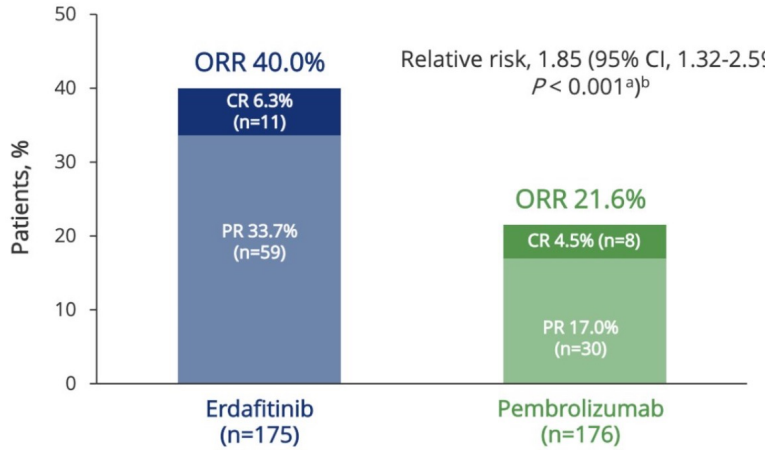
Altération de FGFR :15-20% des patients
Erdafitinib en accès précoce post CT, post IO
40 % ORR, OS 13.8 mois

Y.Loriot ESMO 2022

Métastatique : nouvelles drogues

FGFR : THOR cohorte 2 ERDAFITINIB vs PEMBROLIZUMAB chez FRGFR altéré 2ème L, ESM0 2023

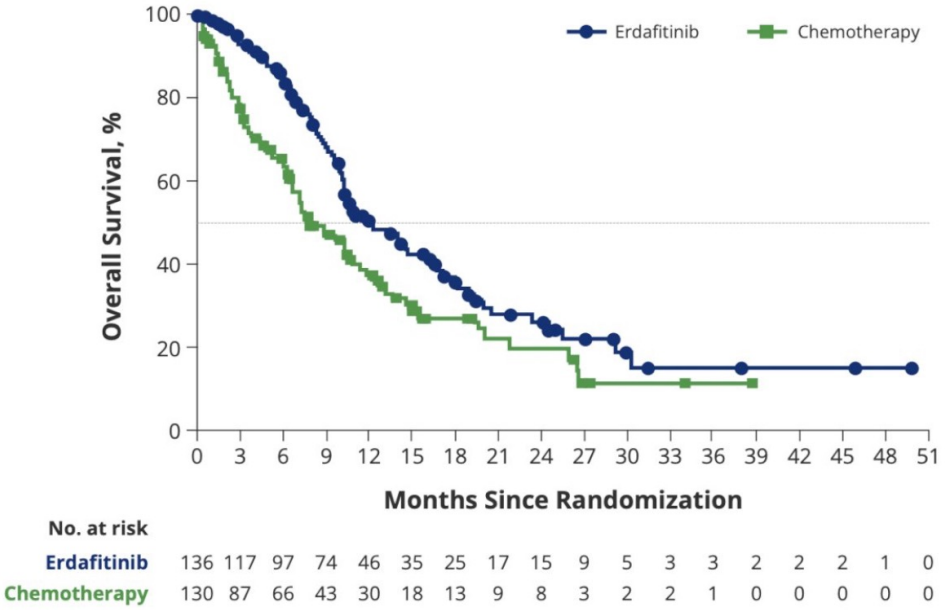


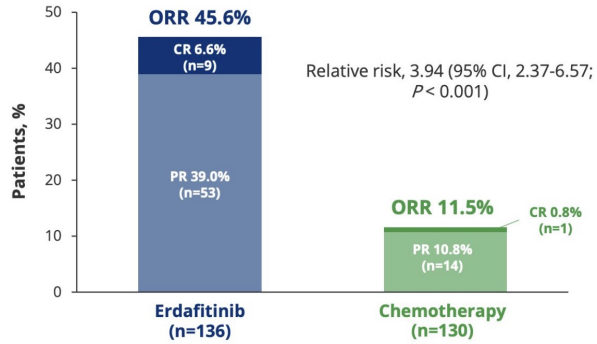


Objectif sur OS non atteint

Métastatique : nouvelles drogues

FGFR : THOR cohorte 1 ERDAFITINIB vs chimiothérapie chez FRGFR altéré post IO, ASCO 2023





Patients with AEs, n (%)[a]	Erdafitinib (n=135)	
	Any grade	Grade 3-4
≥1 treatment-related AE	131 (97.0)	62 (45.9)
Hyperphosphatemia	106 (78.5)	7 (5.2)
Diarrhea	74 (54.8)	4 (3.0)
Stomatitis	62 (45.9)	11 (8.1)
Dry mouth	52 (38.5)	0
PPE syndrome	41 (30.4)	13 (9.6)
Onycholysis	31 (23.0)	8 (5.9)
Patients who discontinued study treatment, n (%)		
Discontinuation due to treatment-related AEs	11 (8.1%)[b]	

- **In the erdafitinib group:**
  - 18 patients (13.3%) had treatment-related serious AEs
  - 1 treatment-related death occurred[c]
  - AEs with erdafitinib were mostly manageable with dose modifications and supportive care
- **In the chemotherapy group:**
  - 27 patients (24.1%) had treatment-related serious AEs
  - 6 treatment-related deaths occurred[d]

Patients with AEs, n (%)[e]	Chemotherapy (n=112)	
	Any grade	Grade 3-4
≥1 treatment-related AE	97 (86.6)	52 (46.4)
Anemia	31 (27.7)	7 (6.3)
Alopecia	24 (21.4)	0
Nausea	22 (19.6)	2 (1.8)
Neutropenia	21 (18.8)	15 (13.4)
Leukopenia	13 (11.6)	9 (8.0)
Febrile neutropenia	9 (8.0)	10 (8.9)
Patients who discontinued study treatment, n (%)		
Discontinuation due to treatment-related AEs	15 (13.4)[f]	

Objectif sur OS atteint, baisse de 36 % du risque de décès

Métastatique : nouvelles drogues

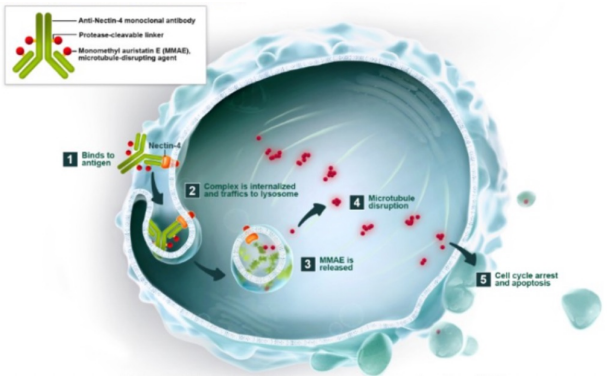
FGFR : NORSE ERDAFITINIB +/- CETRELIMAB 1ère L unfit, phase 2, ASCO 2023

	ERDA+CET (n=44)	ERDA (n=43)
ORR, % (95% CI)	54.5 (38.8, 69.6)	44.2 (29.1, 60.1)
Confirmed CR, n (%)	6 (13.6)	1 (2.3)
DCR, % (95% CI)	79.5 (64.7, 90.2)	88.4 (74.9, 96.1)
Median DOR (95% CI), mo	11.10 (8.77, NE)	9.72 (4.60, NE)
Median PFS (95% CI), mo	10.97 (5.45, 13.63)	5.62 (4.34, 7.36)

Réponse objective…mais ne sera pas développé au-delà

Métastatique : nouvelles drogues

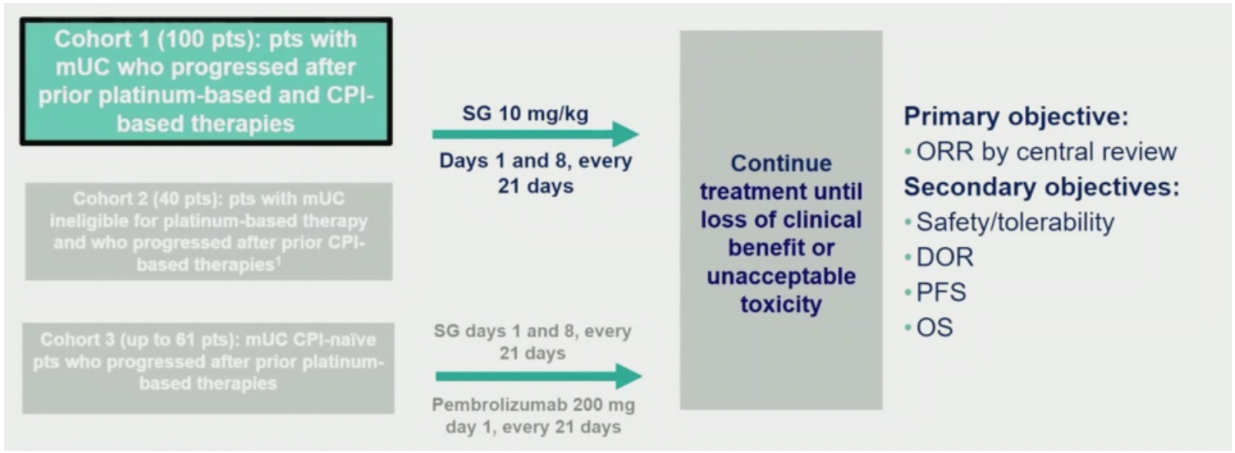
Anticorps conjugués : Nectin-4, Trop-2, HER2



	Enfortumab vedotin	Sacituzumab govitecan	RC-48 (Disitamab vedotin)	DS-801
Target	Nectin-4	Trop-2	HER2	HER2
Linker	cleavable	Cleavable	cleavable	cleavable
Payload	MMAE	SN-38	MMAE	Deruxtecan (DNA topo I inh)
Indication	Post platinum and PD(L)1 mUC Ineligible for CDDP and treated with received 1 or more therapies	Post platinum and PD(L)1 mUC	NA	NA

Métastatique : nouvelles drogues

Sacituzumab Govitecan : TROPHY-U-01, phase II

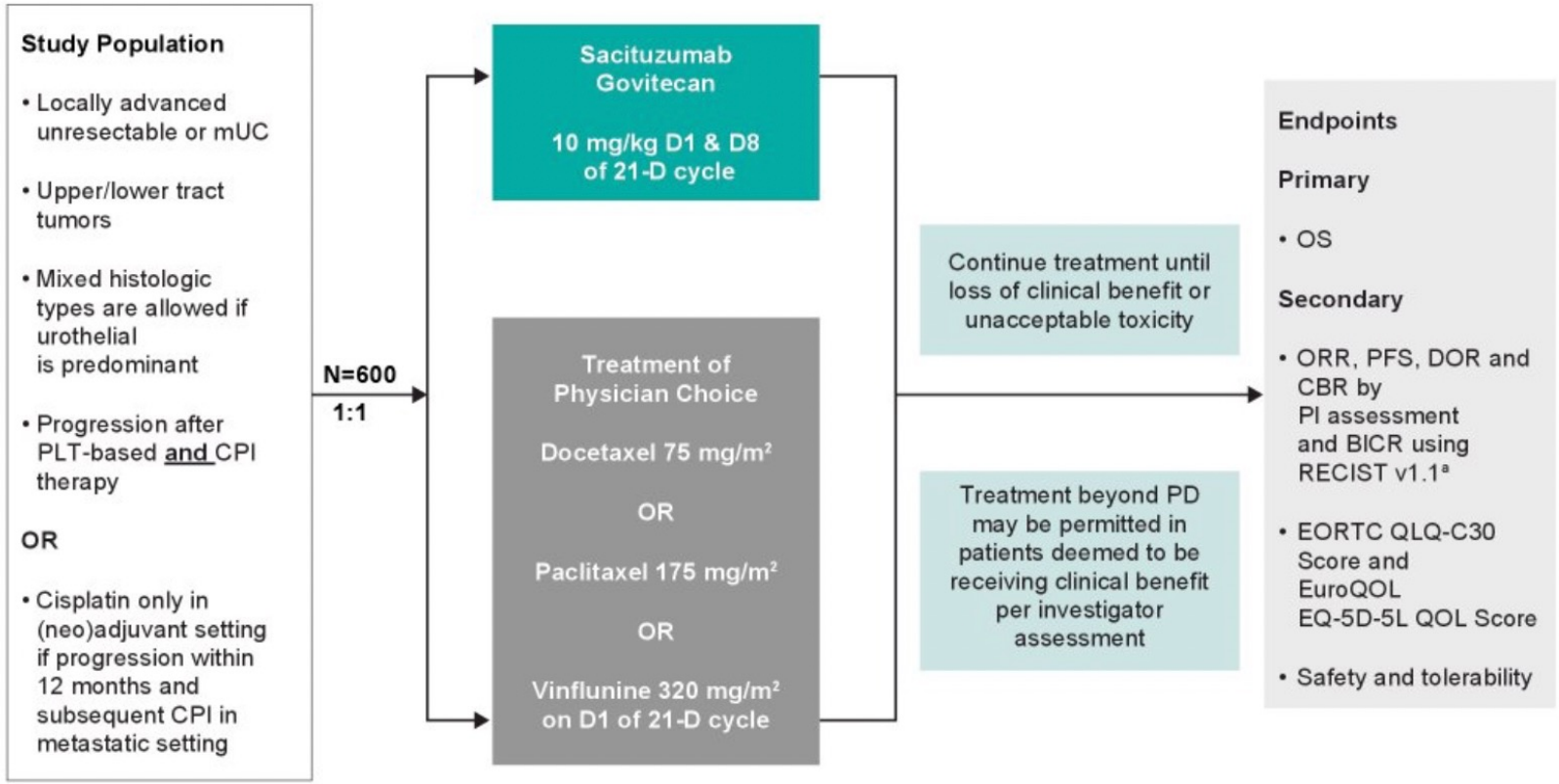


Demande d'approbation accélérée par la FDA

Variable	(N = 113)
Best response, No. (%)	
CR	6 (5)
PR	25 (22)
SD	38 (34)
PD	21 (19)
Not evaluable	8 (7)
Not assessed[a]	15 (13)
ORR	
No. of patients	31
% patients (95% CI)	27 (19 to 37)
CBR[b]	
No. of patients	42
% patients (95% CI)	37 (28 to 47)
Time to onset of response (months)	
Median	1.6
Range	1.2-2.9
Median DOR (months)	
Median	7.2
95% CI	4.7 to 8.6
Range	1.4-13.7

Métastatique : nouvelles drogues

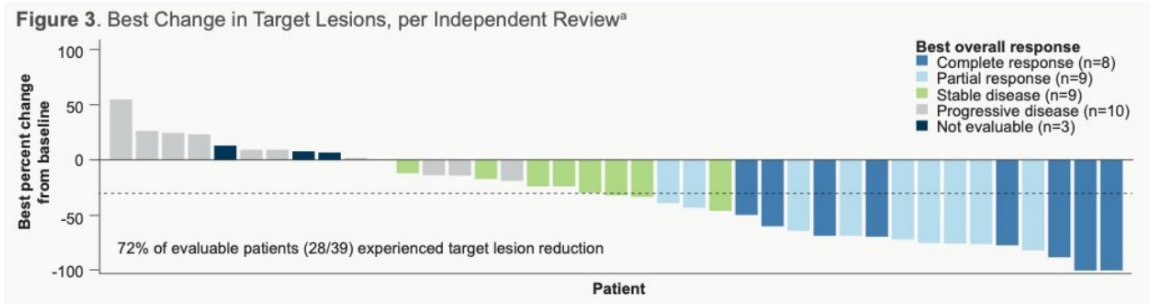
Sacituzumab Govitecan : TROPICS-04

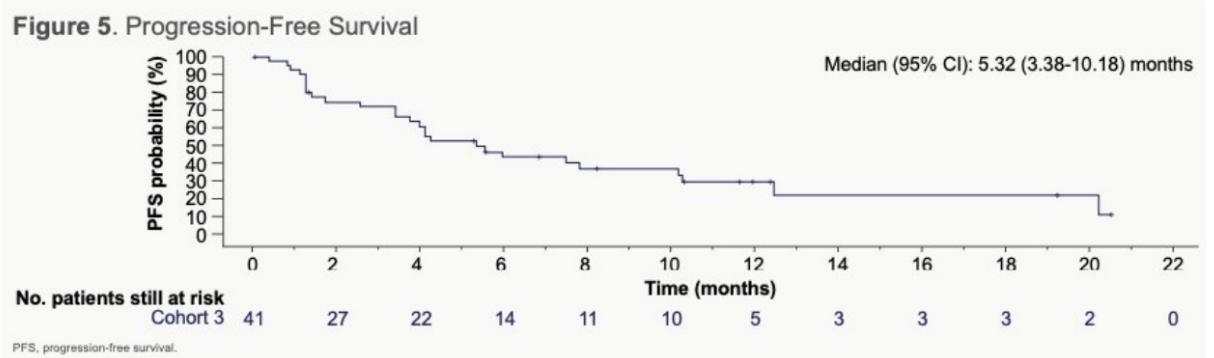


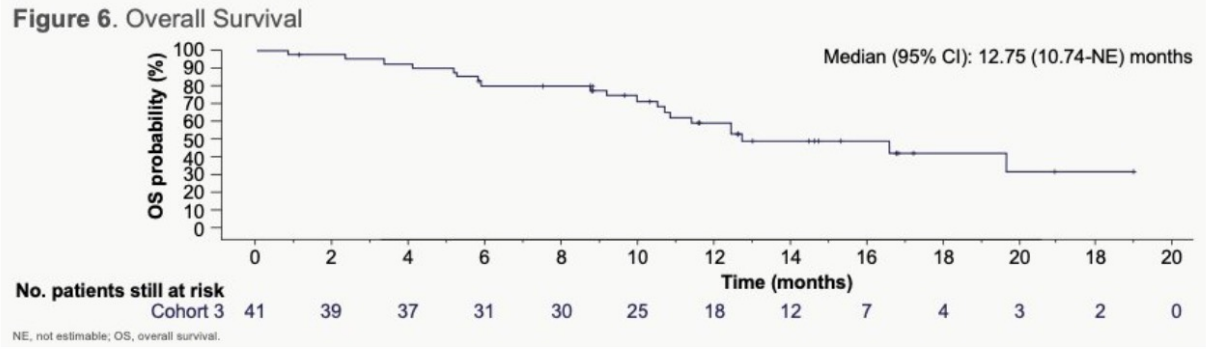
En cours

Métastatique : nouvelles drogues

TROPHY U01 cohorte 3 : Sacituzumab Govitecan + Pembrolizumab en 2ème L platine résistant



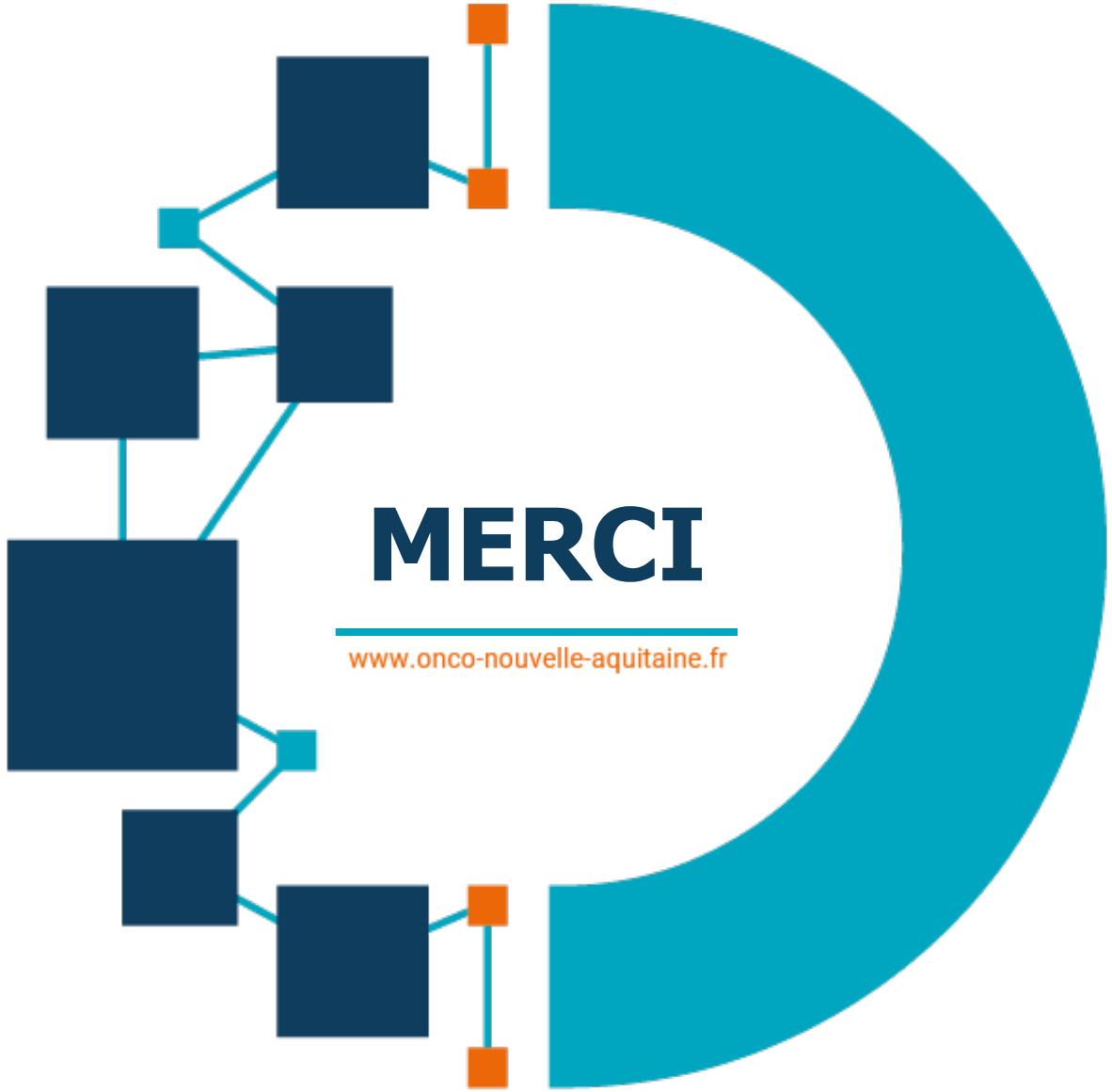




Taux de réponse intéressant chez une population résistante au platine
A voir comment cela pourra être intégrer aux nouveaux référentiels

Conclusions

- Chimiothérapie néoadjuvante ++ : MVAC dd> GC
- Développement des immunothérapies et ADC en péri-opératoire
- Développement des stratégies de préservation de vessie : en cours
- Nouvelles cibles : FGFR 3ème L, sacituzumab govitecan, HER2…
- **Nouveautés 2023 : EV – P en 1ère Ligne ++, CG + NIVO en 1ère L**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