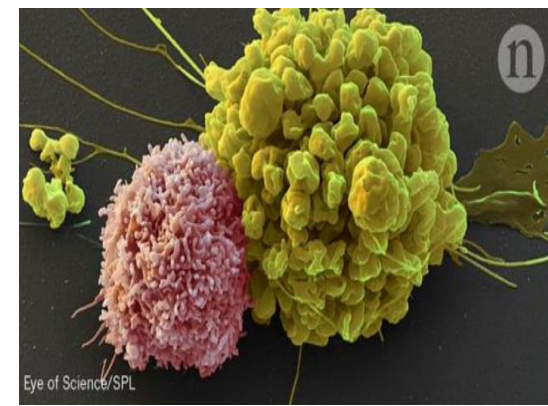




2^{ème} FORUM DES CANCERS UROLOGIQUES

09 et 10 juin 2022, Hôtel Mercure ,Alger



L'immunothérapie dans le cancer urothélial

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Cancer de la vessie

FREQUENT

GRAVE

TRES MUTE

CHIMIOSENSIBLE

RADIOSENSIBLE

IMMUNOSENSIBLE

Introduction

- Le traitement du cancer de la vessie a très peu évolué depuis plusieurs années avec des taux de récurrences et de progression élevés.
- La chimiothérapie à base de cisplatine représente actuellement la première ligne de traitement chez les patients atteints d'un cancer de la vessie métastatique.
- Environ 50 % d'entre eux sont inéligibles pour cette thérapie, généralement à cause d'un mauvais état général.
- En deuxième ligne, une chimiothérapie de carboplatine/gemcitabine peut leur être proposée, avec une efficacité moindre .
- L'immunothérapie a déjà fait ses preuves comme traitement de plusieurs types de cancer et utilisée dans le cancer VNIM de haut grade depuis des décennies

Immunothérapies anti-checkpoints : aspects fondamentaux

Les inhibiteurs de points de contrôle immunitaire (checkpoints inhibiteurs) ouvrent un nouveau chapitre sur le traitement des différents stades du cancer de la vessie, y compris les tumeurs musculo-invasives et métastatiques, offrant des perspectives thérapeutiques, capables de révolutionner la prise en charge

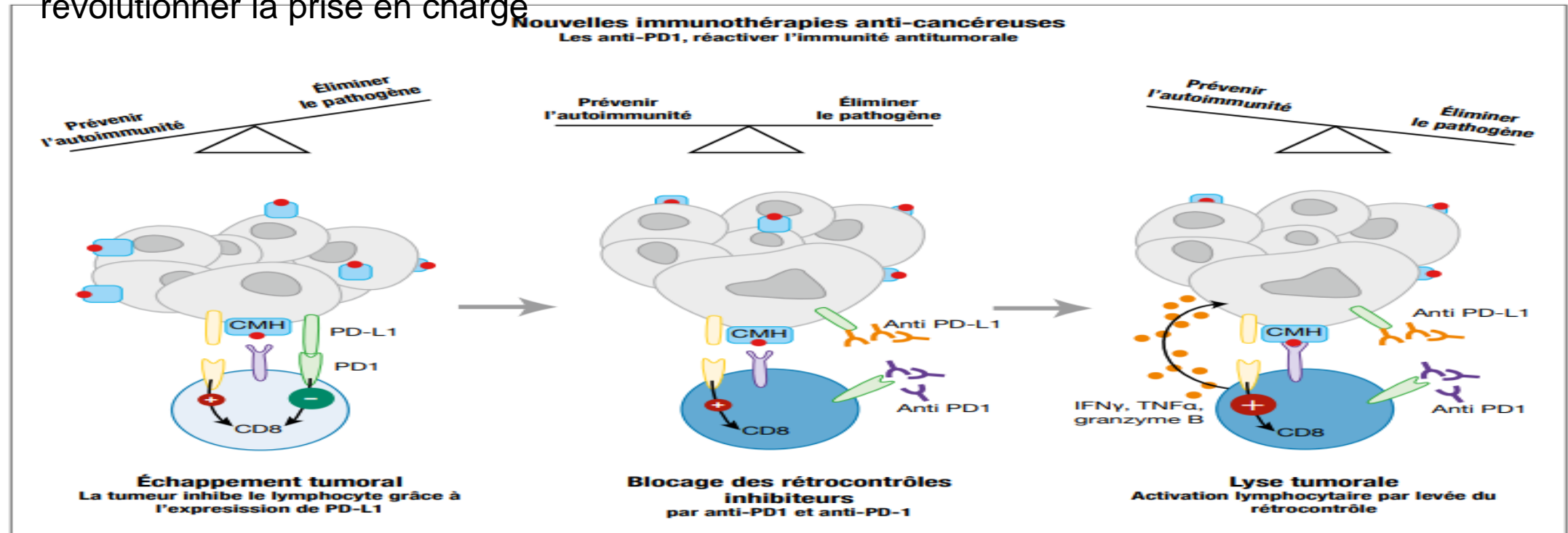
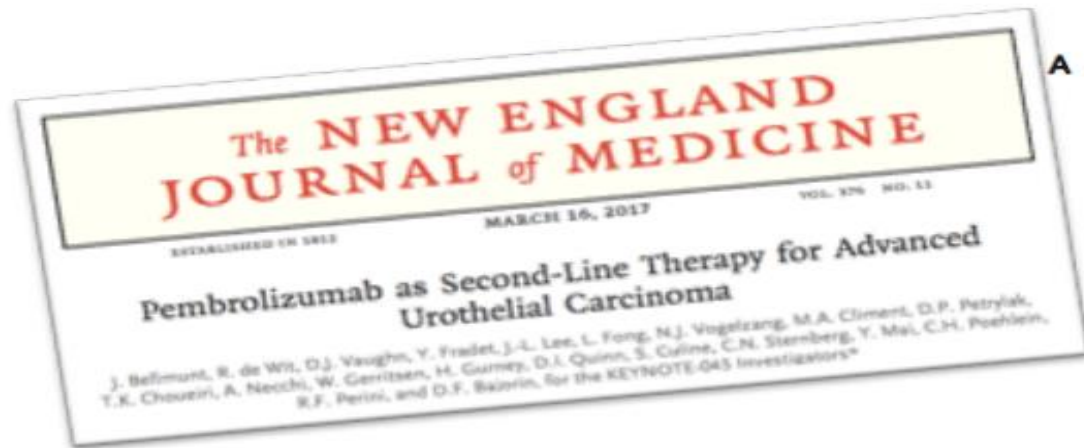
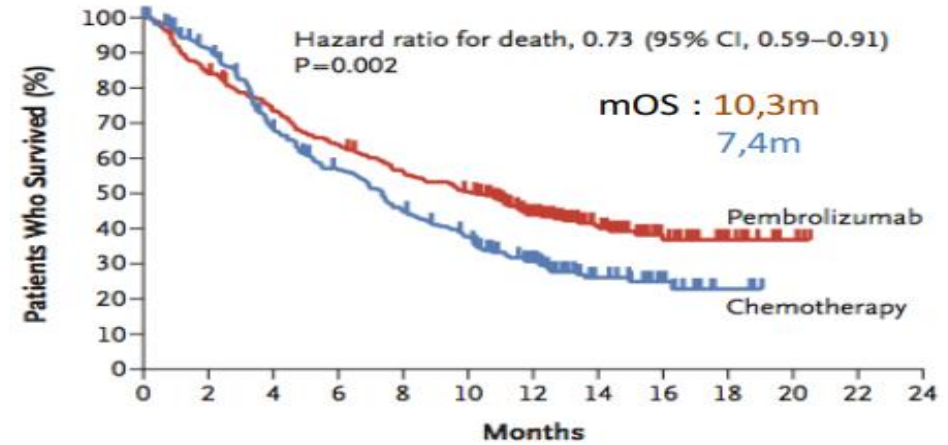


Figure 4. Mode d'action des anti-PD-1/PD-L1.

Pembrolizumab : essai transformé!



A Overall Survival



No. at Risk

Pembrolizumab	270	226	194	169	147	131	87	54	27	13	4	0	0
Chemotherapy	272	232	171	138	109	89	55	27	14	3	0	0	0



AMM FDA et EMA



France : prix en attente (compassionnel en cours)

SECOND LINE PHASE III

KEYNOTE-045 Study Design (NCT02256436)

- Urothelial cancer
- Progression or recurrence of urothelial cancer following a first-line platinum-containing regimen.
- No more than 2 prior lines of systemic chemotherapy.

Randomization
N = 470 patients

Estimated timelines
Estimated completion: May 2017

Pembrolizumab

SOC:
Paclitaxel,
Docetaxel or
Vinflunine

Primary end points
OS & PFS

Secondary end points
• ORR
• Safety

IMvigor211 Study Design (NCT02302807)

- Urothelial cancer
- Progression or recurrence of urothelial cancer following a first-line platinum-containing regimen.

Randomization
N = 932 patients

Estimated timelines
Estimated completion: Nov 2017

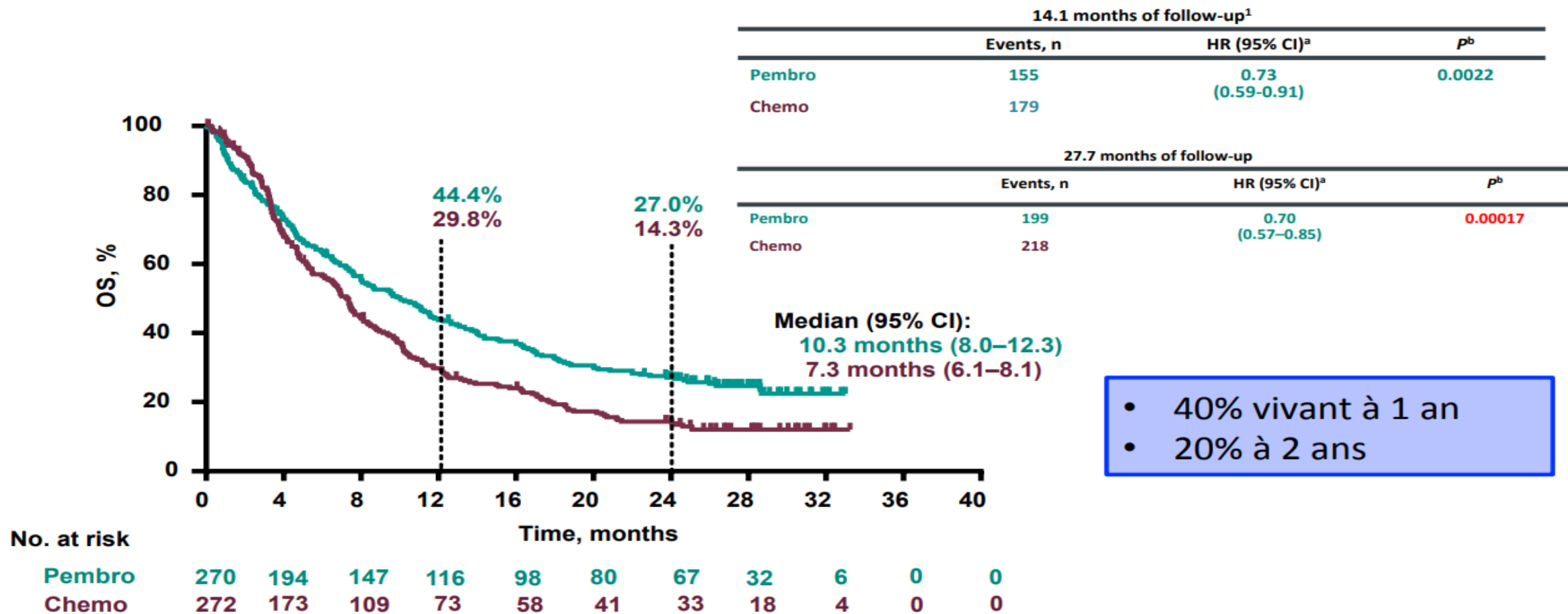
Atezolizumab

SOC:
Docetaxel,
Paclitaxel or
Vinflunine

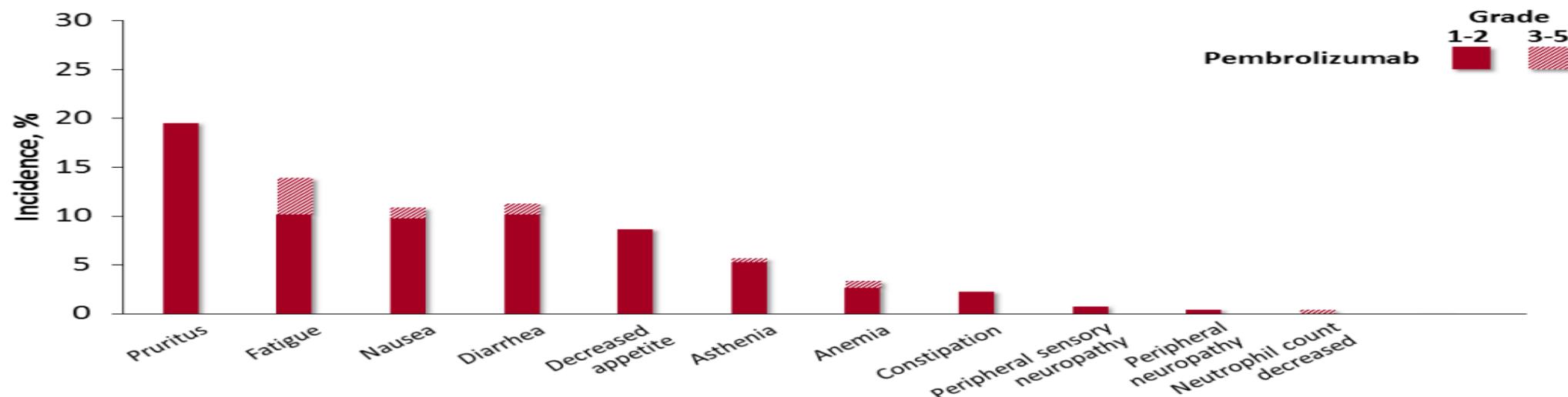
Primary end points
OS

Secondary end points
• ORR
• PFS
• DOR
• Safety

KENOYTE-045: pembrolizumab

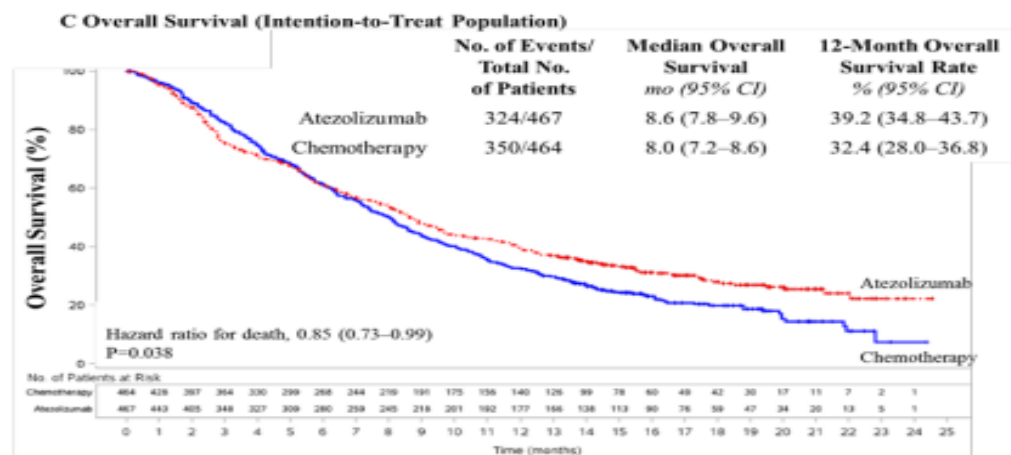
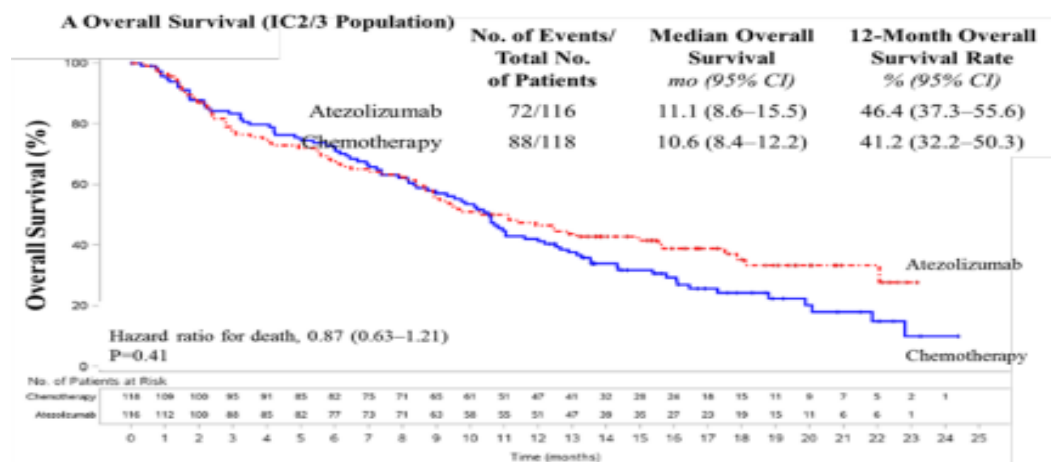


TOLERANCE



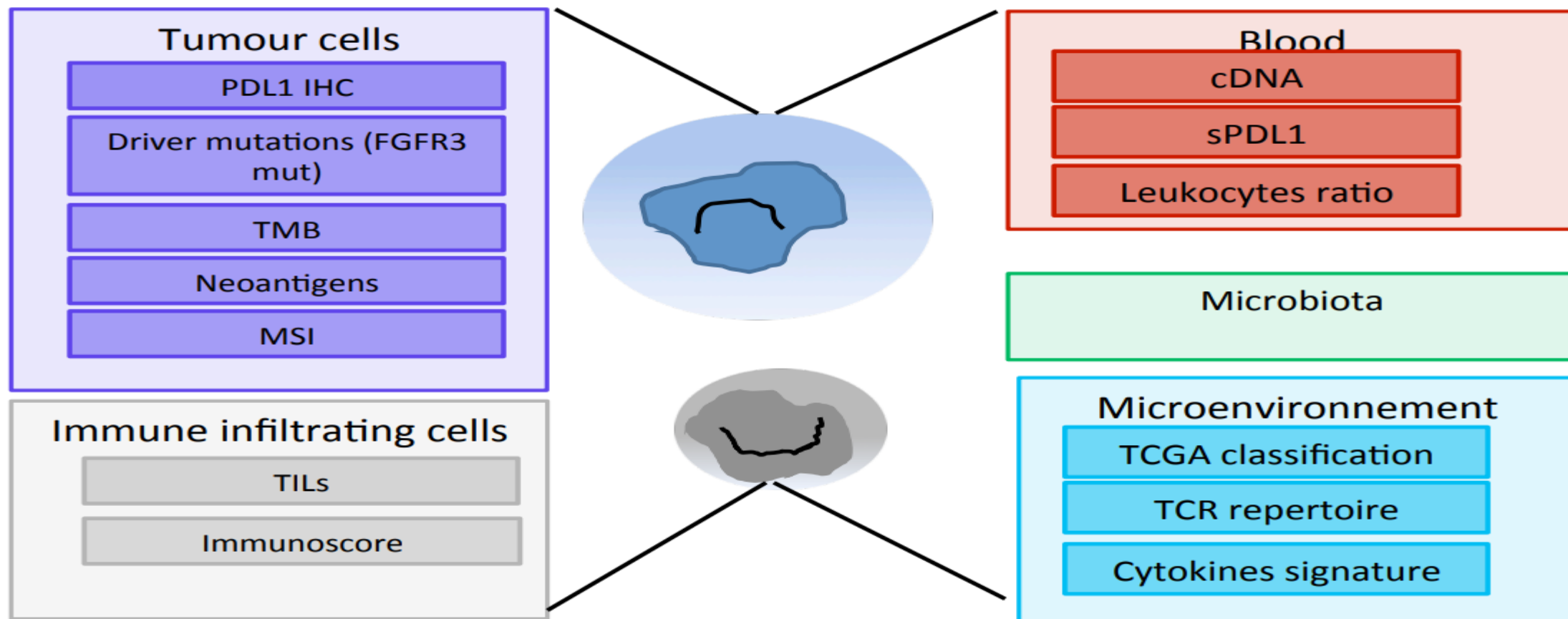
	Pembrolizumab N = 266	Chemotherapy N = 255
Exposure, median (range)	3.5 mo (0.03-20.0)	1.5 mo (0.03-14.2)
Treatment-related AEs, n (%)	162 (60.9)	230 (90.2)
Grade 3-5	40 (15.0)	126 (49.4)
Serious	27 (10.2)	57 (22.4)
Discontinuation	15 (5.6)	28 (11.0)
Grade 5	4 (1.5)	4 (1.6)

IMVIGOR 211 study



ORR: 13.4% ITT and 23% in IC 2/3
1-year OS : 40% in ITT patients

Potentiels biomarqueurs en L2



PRINCIPLES OF SYSTEMIC THERAPY

Second-line systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)^{d,e} Participation in clinical trials of new agents is recommended.	
Preferred regimen • Pembrolizumab (category 1) ¹⁹	Other recommended regimens • Paclitaxel ²⁵ or docetaxel ²⁶ • Gemcitabine ¹⁵
Alternative preferred regimens • Immune checkpoint inhibitor ▶ Nivolumab ²⁰ ▶ Avelumab ^{21,22} • Erdafitinib ^{f,23} • Enfortumab vedotin-ejfv ^{9,24}	Useful in certain circumstances based on prior medical therapy • Ifosfamide, doxorubicin, and gemcitabine ¹⁷ • Gemcitabine and paclitaxel ¹⁶ • Gemcitabine and cisplatin ⁴ • DDMVAC with growth factor support ²

Second-line systemic therapy for locally advanced or metastatic disease (Stage IV) (post-checkpoint inhibitor) Participation in clinical trials of new agents is recommended.	
Preferred regimens for cisplatin ineligible, chemotherapy naïve • Enfortumab vedotin-ejfv ²⁴ • Gemcitabine/carboplatin	Other recommended regimens • Erdafitinib ^{f,23} • Paclitaxel or docetaxel ²⁶ • Gemcitabine ¹⁵
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin ⁴ • DDMVAC with growth factor support ²	Useful in certain circumstances based on prior medical therapy • Ifosfamide, doxorubicin, and gemcitabine ¹⁷ • Gemcitabine and paclitaxel ¹⁶

L'IMMUNOTHÉRAPIE DANS LE STADE AVANCÉ (MÉTASTATIQUE OU NON RÉSÉCABLE) : LE CHALLENGE DES PATIENTS INÉLIGIBLES A LA CISPLATINE

Critères de non-éligibilité au cisplatine

Patients meeting at least one of the following are considered 'unfit'

- WHO or ECOG performance status of 2, or Karnofsky performance status of 60–70%
- Creatinine clearance (calculated or measured) less than 1 mL/s
- CTCAE version 4, grade 2 or above audiometric hearing loss
- CTCAE version 4, grade 2 or above peripheral neuropathy
- NYHA class III heart failure

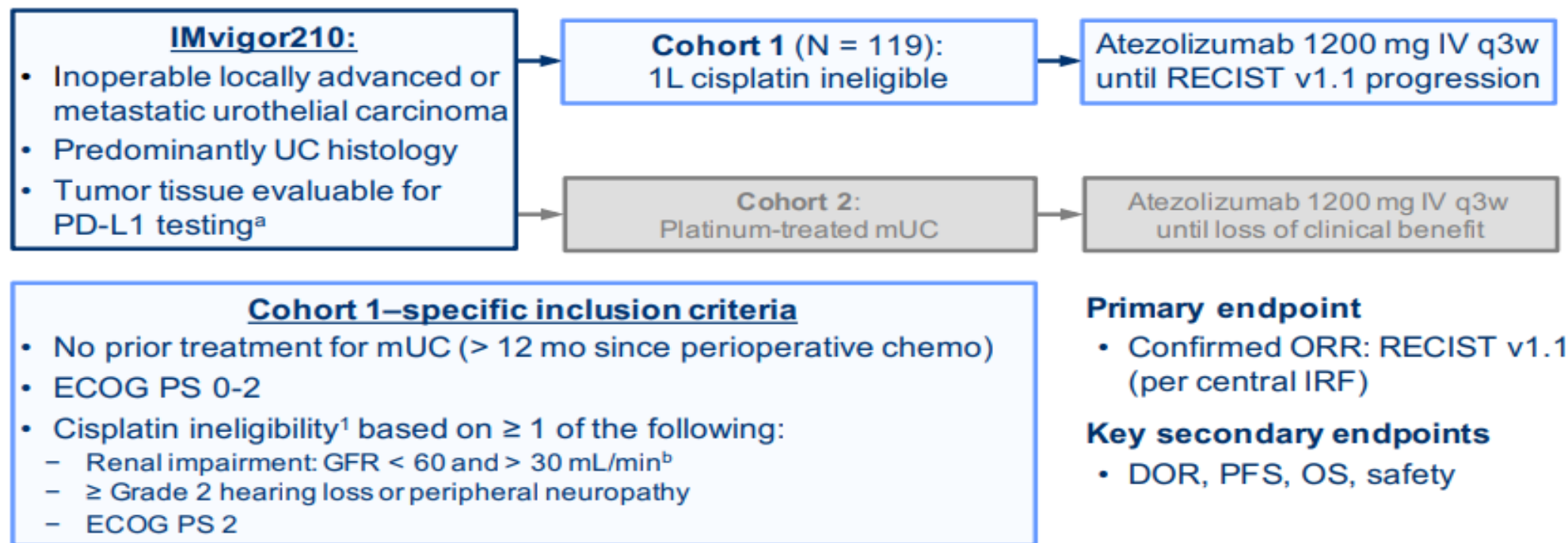
30–50% des patients métastatiques sont inéligibles au cisplatine

Perspectives en 1ère ligne

INELIGIBLES AU CISPLATINE			
	Atézolizumab phase 2	Pembrolizumab phase 2	CT à base de CARBOPLATINE ³
Etude	IMVIGOR 210¹	KEYNOTE 052²	
N	119	370	
Inéligibilité au cisplatine - DFG 30-60ml/min - EGOG PS 2 - DFG + PS	70% 20% 7%	49% 32% 9%	
Réponse	23% IC 1/2/3 24% IC 2/3 28% IC 0 21%	24% PD-L1 >10% 37%	28 – 56% ⁴
Délai de réponse	2,1m	2m	
Durée de réponse	Non atteint	Non atteint	
SSP	2,7m	2m	7,7m
SG (ITT)	15,9m	ND	9,8m
EI G3-4 (traitement)	16%	15%	>40%

1- Balman AV et al, Lancet 2017; 2- Balman AV et al, Lancet Oncol 2017; 3- Dogliotti L et al, Eur Urol 2007;
4- Galsky MD et al, Annals Oncol 2012

IMvigor210 Study: Cohort 1



IMvigor210 Study:

Efficacy

Response to atezolizumab (IRF RECIST v1.1)

	IC2/3 (n = 32)	IC1/2/3 (n = 80)	All Patients (N = 119)	IC1 (n = 48)	IC0 (n = 39)
ORR ^a (95% CI)	28% (14, 47)	25% (16, 36)	24% (16, 32)	23% (12, 37)	21% (9, 36)
CR	6%	6%	7%	6%	8%
PR	22%	19%	17%	17%	13%

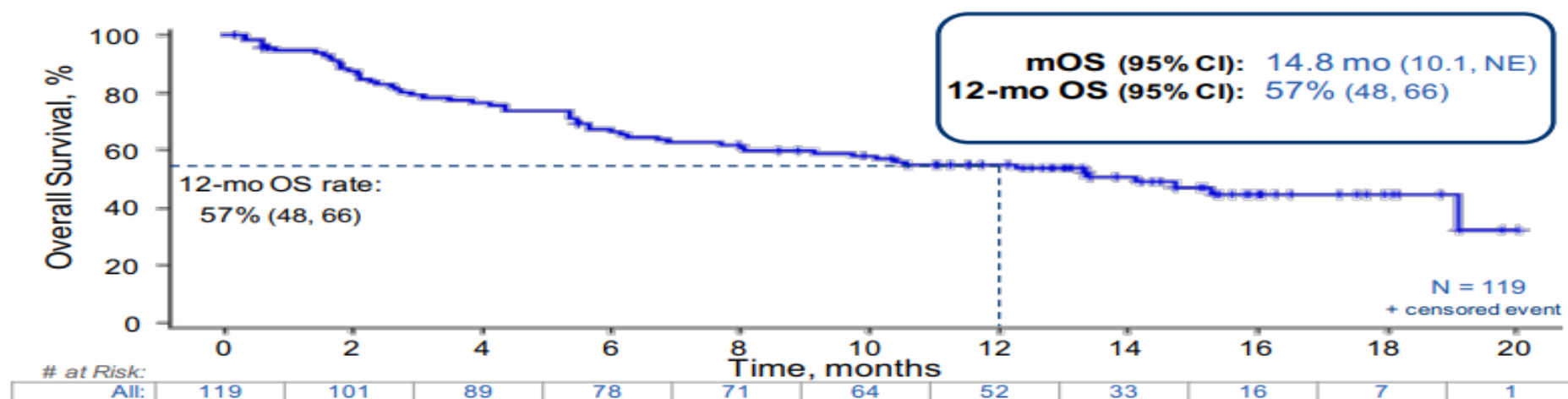
- Patients in this analysis had a median of follow-up duration of 14.4 mo (range, 0.2-20.1 mo)

^a Includes 19 patients with missing/unevaluable responses. All treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1. PD-L1 IC status: IC2/3 (≥5%), IC1 (≥ 1% and < 5%), IC0 (< 1%). Data cutoff: March 14, 2016.

IMvigor210 Study:

Efficacy

Overall Survival (Median and Landmark 12-Month OS)



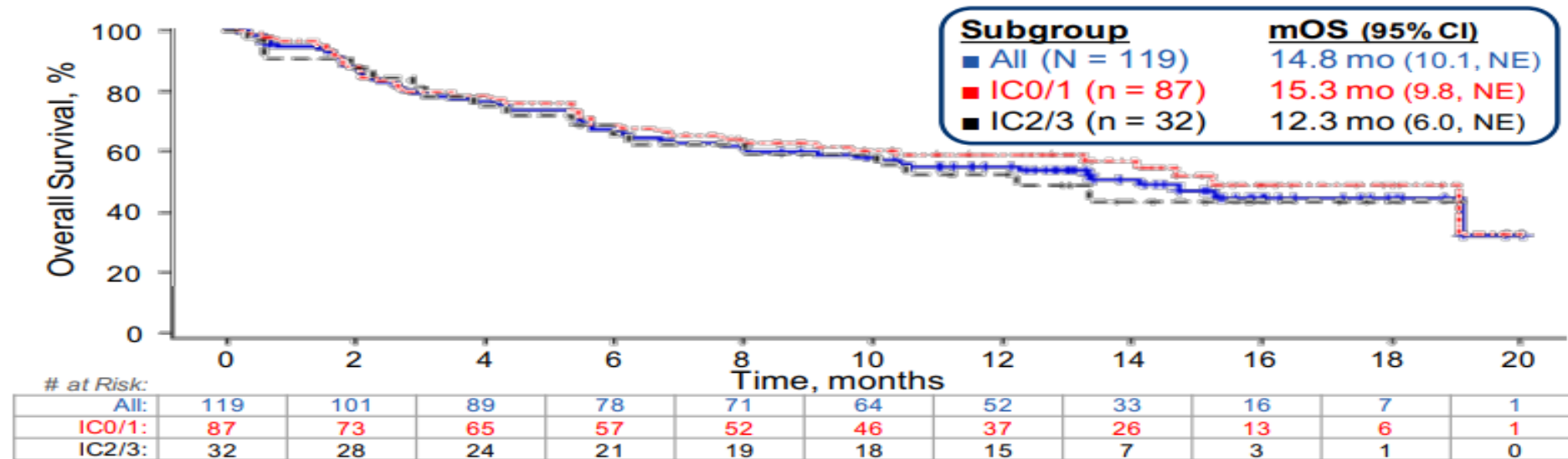
- With a median follow-up of 14.4 months,^a the event rate is 47%
- Atezolizumab compares favorably with historic data from cisplatin-ineligible patients, both from clinical trials and real-world studies^{1,2}

Range, 0.2 to 20.1 mo. Data cutoff: March 14, 2016. 1. De Santis J Clin Oncol 2012. 2. Galsky ECC 2015 [poster 115].

IMvigor210 Study:

Efficacy

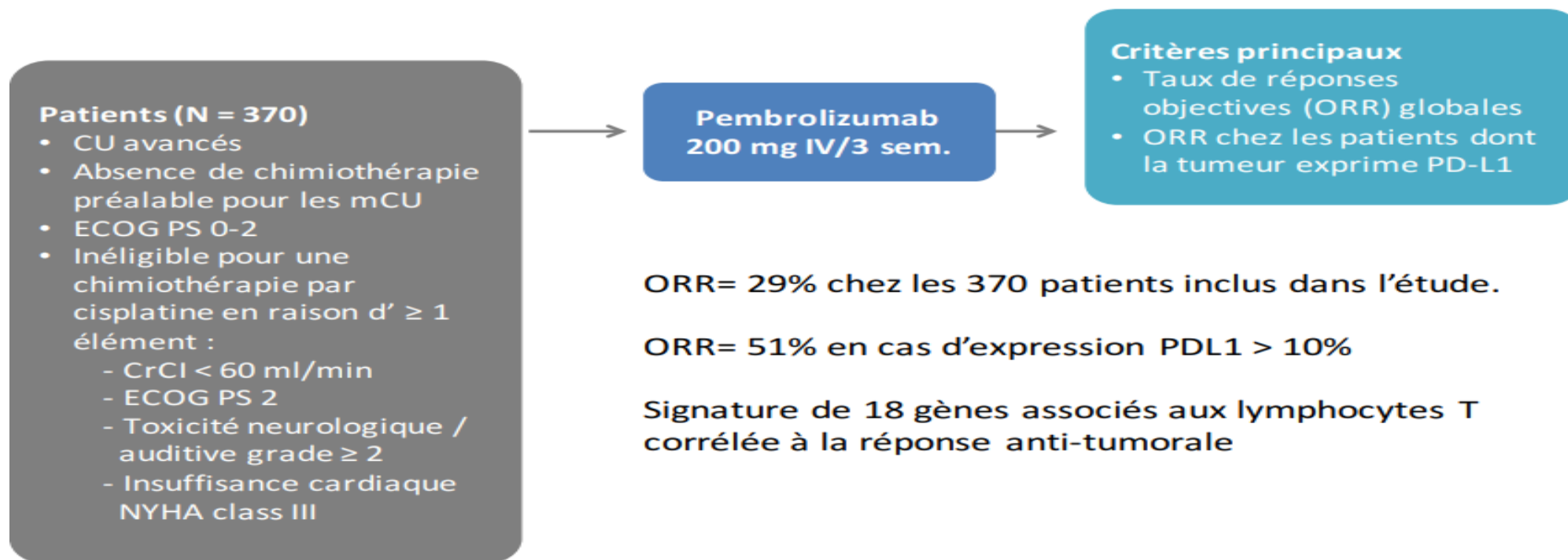
Overall Survival (Median OS) by PD-L1 Status



- With a median follow-up of 14.4 months,^a the event rate is 47%

^a Range, 0.2 to 20.1 mo. Data cutoff: March 14, 2016

KEYNOTE-052 : Pembrolizumab as 1st line



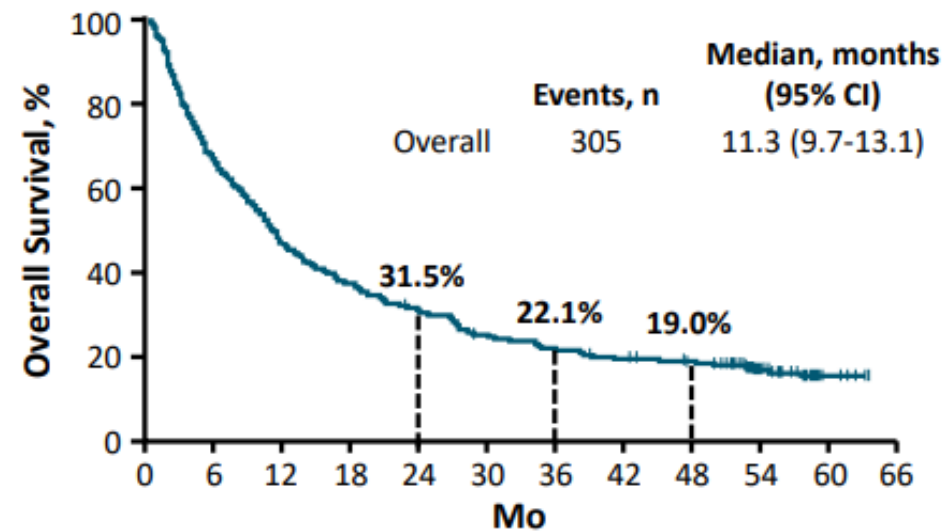
KEYNOTE-052 5-Yr Update: Single-Agent Pembrolizumab in Locally Advanced mUC

- Multisite, single-arm, open-label phase II trial

Inclusion criteria

Patients with locally advanced/metastatic urothelial cancer with measurable disease; no prior systemic chemotherapy and cisplatin-ineligible; ECOG PS 0-2 (N = 370)

- Primary endpoint:** confirmed ORR per RECIST v1.1 by IRR
- Secondary endpoints:** PFS, DoR per RECIST v1.1 by IRR, OS, safety
- Endpoints analyzed in full population and subgroups with PD-L1 CPS* ≥ 10 and CPS* < 10



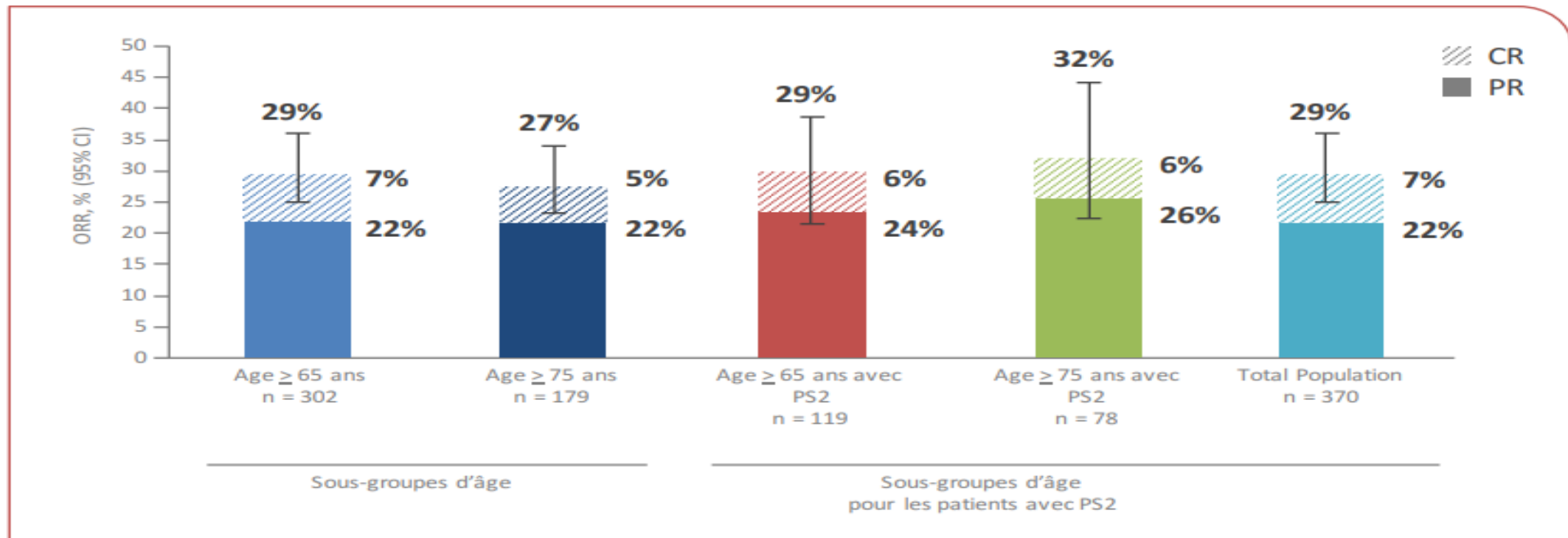
Response, n (%)	Pembrolizumab		
	All (N = 370)	CPS ≥ 10 (n = 110)	CPS < 10 (n = 251)
ORR	107 (28.9)	52 (47.3)	52 (20.7)
▪ CR	35 (9.5)	23 (20.9)	10 (4.0)

*Defined as number of PD-L1–staining cells divided by total number of viable tumor cells x100.



KEYNOTE 052 - Pembrolizumab chez les patients âgés avec un PS 2

Taux de réponse objective (RECIST v1.1) en fonction de l'âge et du PS



Pas de différence de toxicité

Le statut PDL1 requis pour le pembrolizumab et l'atezolizumab en 1L pour les patients inéligibles



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 June 2018
EMA/364553/2018

EMA restricts use of Keytruda and Tecentriq in bladder cancer

Data show lower survival in some patients with low levels of cancer protein PD-L1

Early data from two clinical trials¹ show reduced survival with Keytruda (pembrolizumab) and Tecentriq (atezolizumab) when used as first-line treatments for urothelial cancer (cancer of the bladder and urinary tract) in patients with low levels of a protein called PD-L1. The data indicate that Keytruda and Tecentriq may not work as well as chemotherapy medicines in this group of patients.

As a result, the European Medicines Agency (EMA) has recommended restricting the use of these medicines as first line-treatments for urothelial cancer.

Keytruda and Tecentriq should now only be used for first-line treatment of urothelial cancer in patients with high levels of PD-L1 (see full indications below).

FDA limits the use of Tecentriq and Keytruda for some urothelial cancer patients

FDA has limited the use of Tecentriq and Keytruda for patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing therapy.

The Agency took this action on June 19, 2018, due to decreased survival associated with the use of Keytruda (pembrolizumab) or Tecentriq (atezolizumab) as single therapy (monotherapy) compared to platinum-based chemotherapy in clinical trials to treat patients with metastatic urothelial cancer who have not received prior therapy and who have low expression of the protein programmed death ligand 1 (PD-L1).

The labels of both drugs have been revised to reflect the limitation in the indication. The indications read as follows:

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing therapy and whose tumors express PD-L1 (Combined Positive Score ≥ 10), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

TECENTRIQ is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

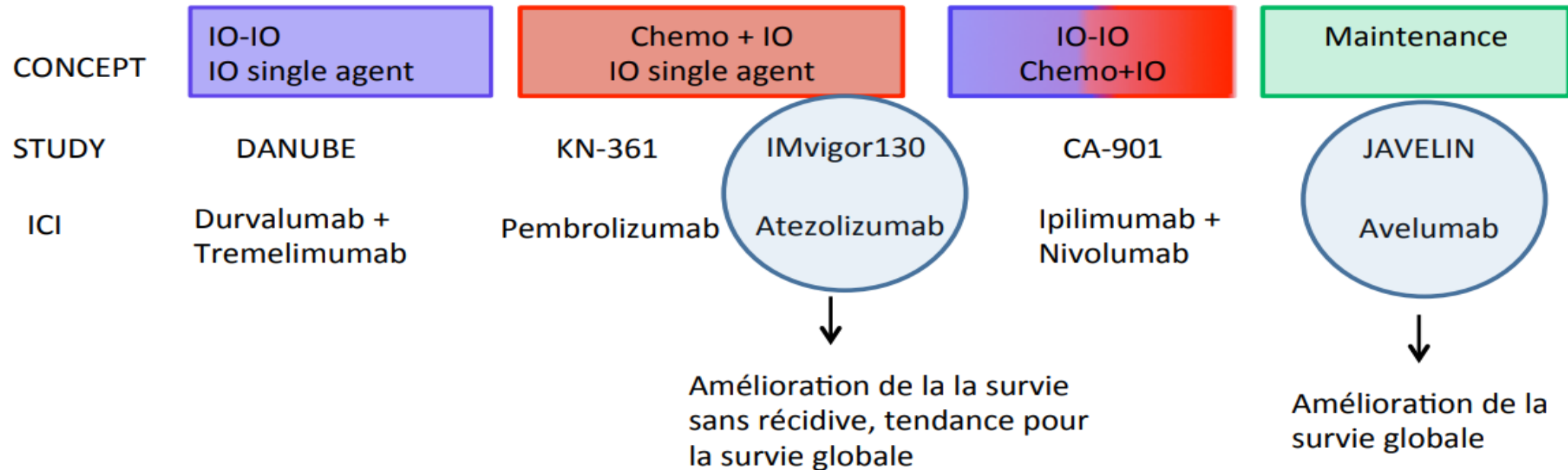
- Are not eligible for cisplatin-containing therapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering $\geq 5\%$ of the tumor area), as determined by an FDA-approved test, or
- Are not eligible for any platinum-containing therapy regardless of PD-L1 status.

On July 2, 2018, the FDA approved the Ventana PD-L1 (SP142) Assay (Ventana Medical Systems, Inc.) for PD-L1 expression in $\geq 5\%$ IC in urothelial carcinoma tissue. The test should be used to select patients with locally advanced or metastatic urothelial carcinoma for treatment with atezolizumab (Tecentriq, Genentech Inc.). The FDA also updated the Prescribing Information for Tecentriq to require use of an FDA-approved test for patient selection.

EMA Press Release 1 June 2018. Available via https://www.ema.europa.eu/documents/press-release/ema-restricts-use-keytruda-tecentriq-bladder-cancer_en.pdf

FDA Press Release 19 June 2018. Available via <https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm612484.htm>

Next step: IO first-line RACE in mUC



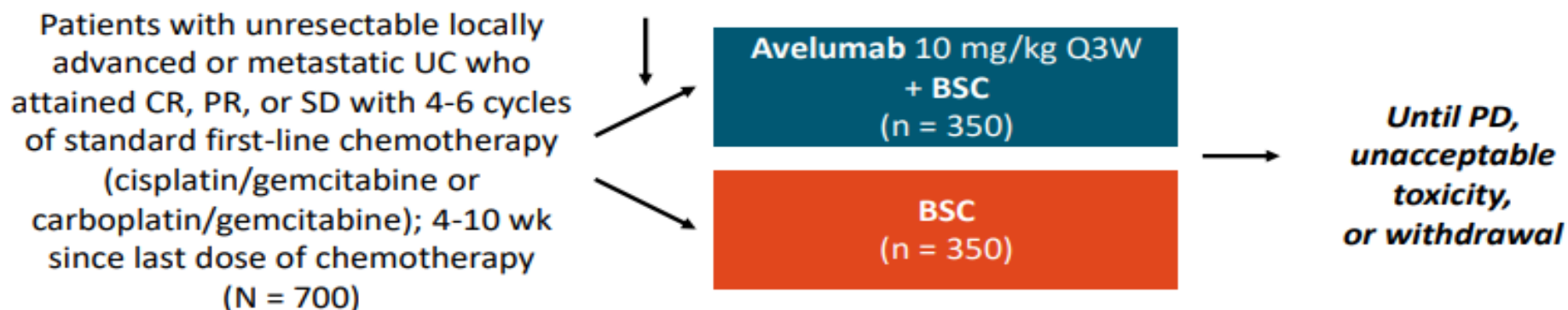
L'IMMUNOTHÉRAPIE DANS LE STADE AVANCÉ (MÉTASTATIQUE OU NON RÉSÉCABLE) : LE CONCEPT DE MAINTENANCE

Le concept de maintenance

JAVELIN Bladder 100: Study Design

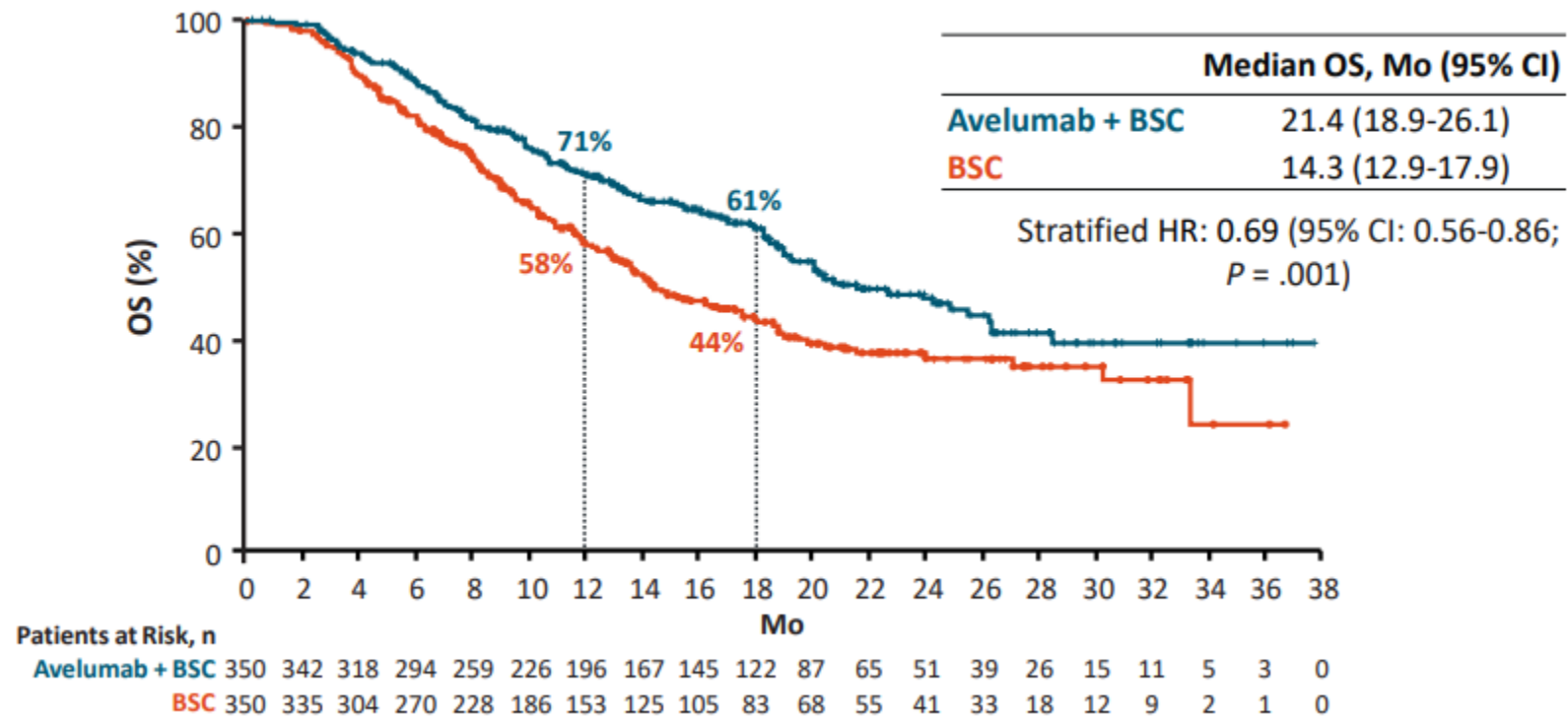
- Randomized, open-label phase III trial (data cutoff: October 21, 2019)

Stratified by best response to first-line chemotherapy (CR or PR vs SD), metastatic site (visceral vs nonvisceral)



- **Primary endpoint:** OS in all randomized patients, PD-L1+ population
 - PD-L1+ status: PD-L1 expression in $\geq 25\%$ of tumor cells, or in $\geq 25\%$ or 100% of tumor-associated immune cells if percentage of immune cells was $> 1\%$ or $\leq 1\%$, respectively
- **Secondary endpoints:** PFS (RECIST v1.1), ORR (RECIST v1.1), safety and tolerability, PROs

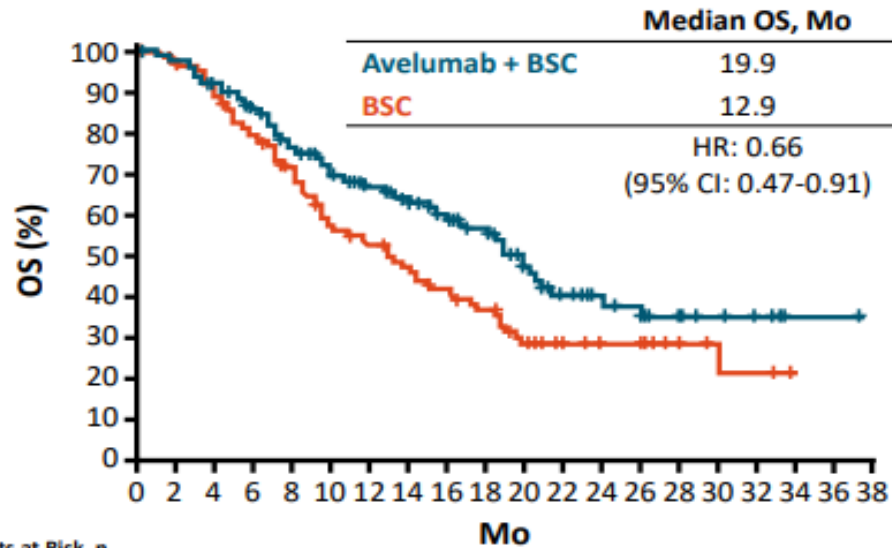
JAVELIN Bladder 100: OS in the Overall Population



OS was measured post-randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function ($P < .0053$).

JAVELIN Bladder 100: Improved OS With First-line Avelumab Maintenance Regardless of First-line CT

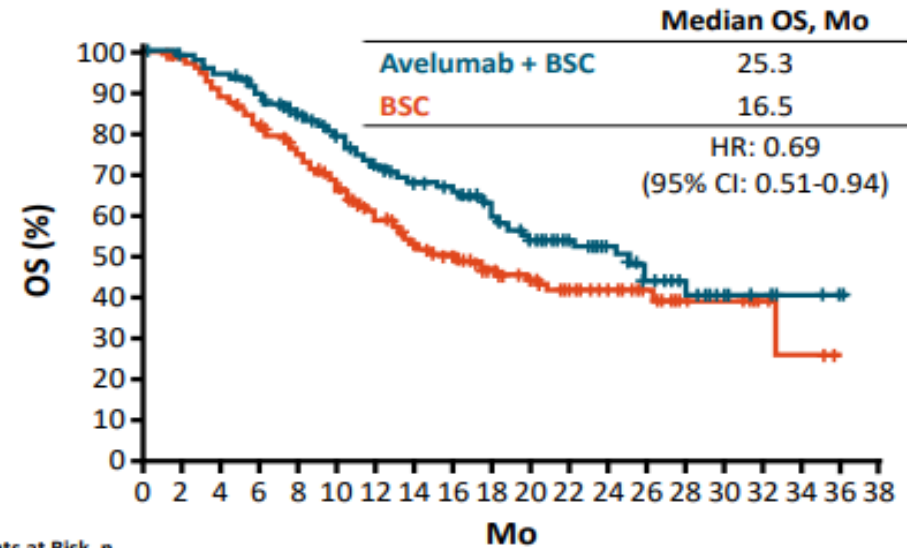
OS With 1L Gemcitabine + Carboplatin (n = 269)



Patients at Risk, n

Avelumab + BSC	147	142	130	119	102	88	78	68	59	48	32	21	16	14	9	6	5	1	1	0
BSC	122	114	104	91	72	57	52	42	36	29	20	15	13	12	6	3	3	3	0	0

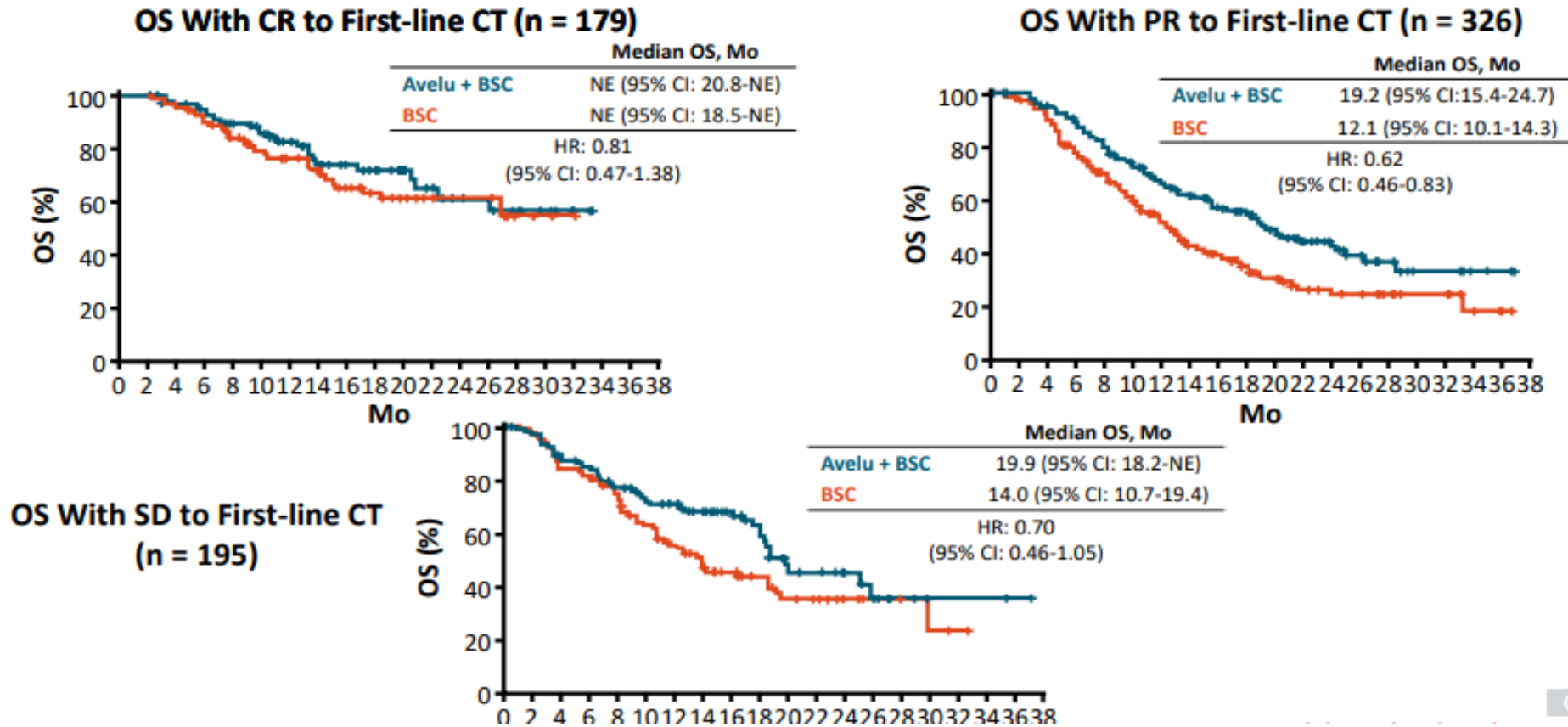
OS With 1L Gemcitabine + Cisplatin (n = 389)



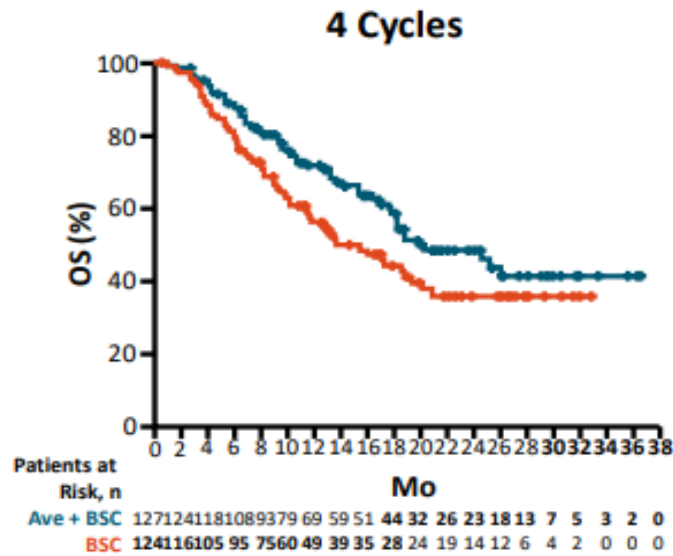
Patients at Risk, n

Avelumab + BSC	183	180	169	157	141	122	103	89	77	66	49	38	32	22	14	8	5	3	2	0
BSC	206	199	182	165	142	116	92	76	63	48	42	34	23	17	11	8	6	2	1	0

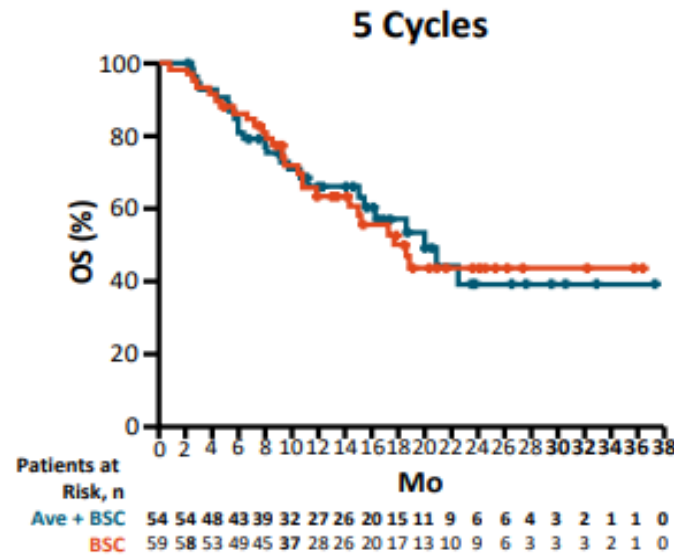
JAVELIN Bladder 100: OS With First-Line Avelumab According to Response to First-Line CT



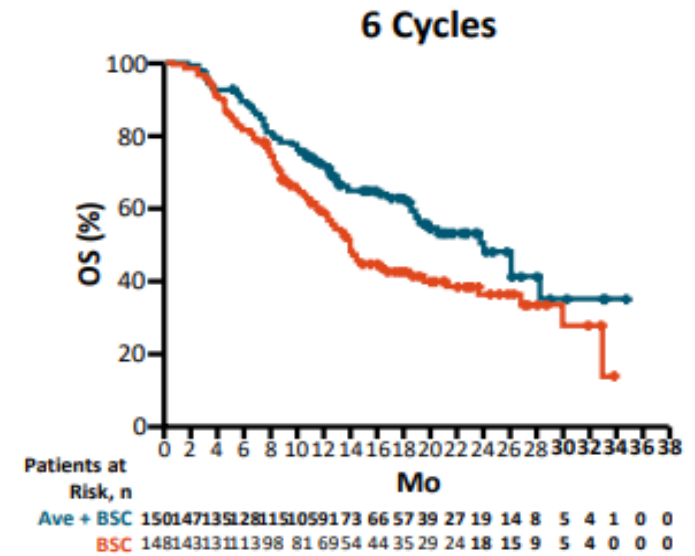
JAVELIN Bladder 100: OS by Number of Cycles of First-line Chemotherapy



Outcome w/4 Cycles	Ave + BSC (n = 127)	BSC (n = 124)
Events, n	54	62
mOS, mo	19.9	13.7
HR (95% CI)	0.69 (0.481-1.000)	

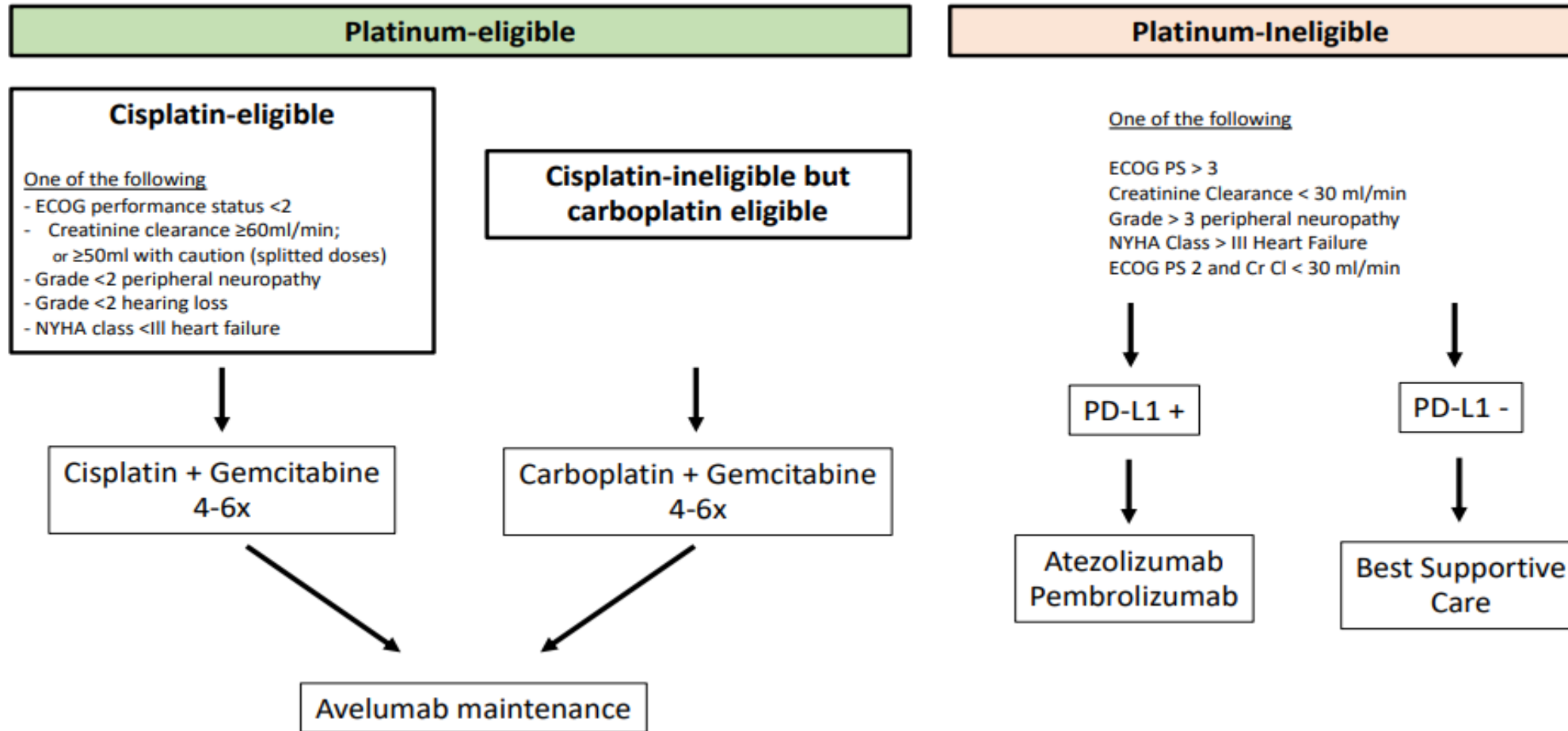


Outcome w/5 Cycles	Ave + BSC (n = 54)	BSC (n = 59)
Events, n	24	27
mOS, mo	19.9	17.8
HR (95% CI)	0.98 (0.568-1.707)	



Outcome w/6 Cycles	Ave + BSC (n = 150)	BSC (n = 148)
Events, n	63	80
mOS, mo	24.0	14.0
HR (95% CI)	0.66 (0.472-0.915)	

Algorithme décisionnel dans la première ligne de traitement du carcinome urothélial métastatique ou non résecable





PRINCIPLES OF SYSTEMIC THERAPY

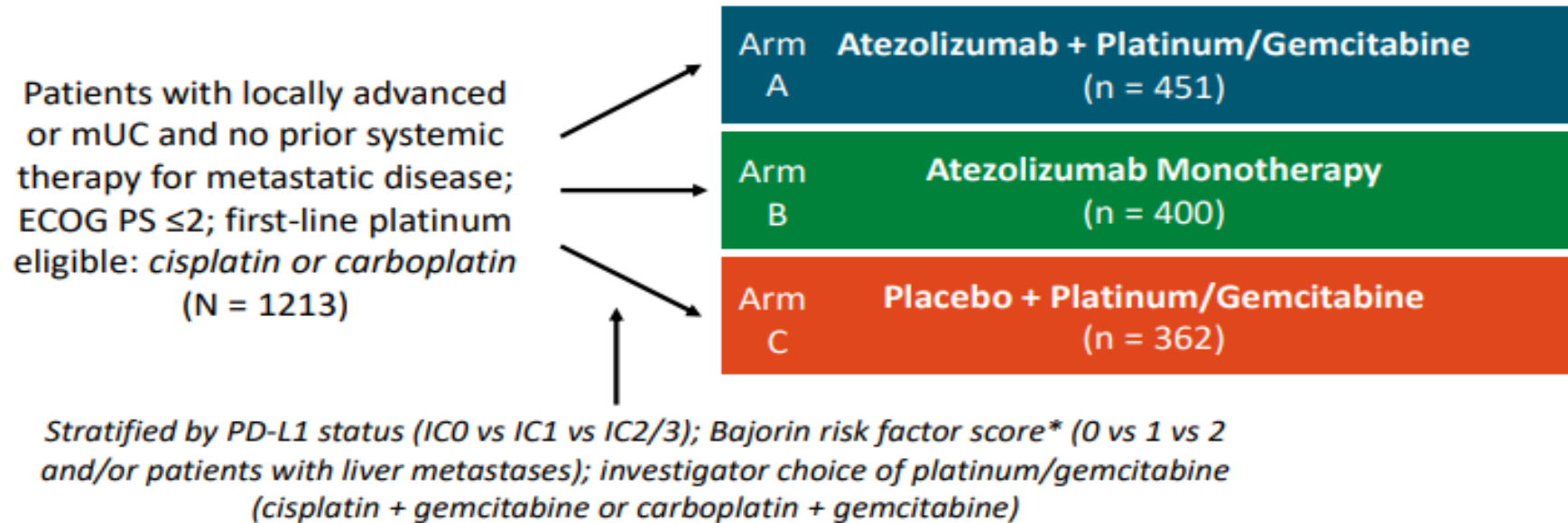
First-line systemic therapy for locally advanced or metastatic disease (Stage IV)	
Cisplatin eligible	<p>Preferred regimens</p> <ul style="list-style-type: none"> • Gemcitabine and cisplatin⁴ (category 1) followed by avelumab maintenance therapy (category 1)^{a,11} • DDMVAC with growth factor support (category 1)^{2,8} followed by avelumab maintenance therapy (category 1)^{a,11}
Cisplatin ineligible	<p>Preferred regimens</p> <ul style="list-style-type: none"> • Gemcitabine and carboplatin¹² followed by avelumab maintenance therapy (category 1)^{a,11} • Atezolizumab¹³ (only for patients whose tumors express PD-L1^b or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) • Pembrolizumab¹⁴ (only for patients whose tumors express PD-L1^c or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) <p>Other recommended regimens</p> <ul style="list-style-type: none"> • Gemcitabine¹⁵ • Gemcitabine and paclitaxel¹⁶ <p>Useful under certain circumstances</p> <ul style="list-style-type: none"> • Ifosfamide, doxorubicin, and gemcitabine¹⁷ (for patients with good kidney function and good PS)

- The presence of both non-nodal metastases and ECOG performance score ≥ 2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.¹⁸
- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
 - ▶ Participation in clinical trials of new or more tolerable therapy is recommended.

Chemotherapy + Immunotherapy vs Chemotherapy

AMÉLIORER LA PREMIÈRE LIGNE DE TRAITEMENT, ASSOCIATION OU MONOTHÉRAPIE?

Phase III IMvigor130: Atezolizumab ± Platinum-Based Chemotherapy for First-line Patients

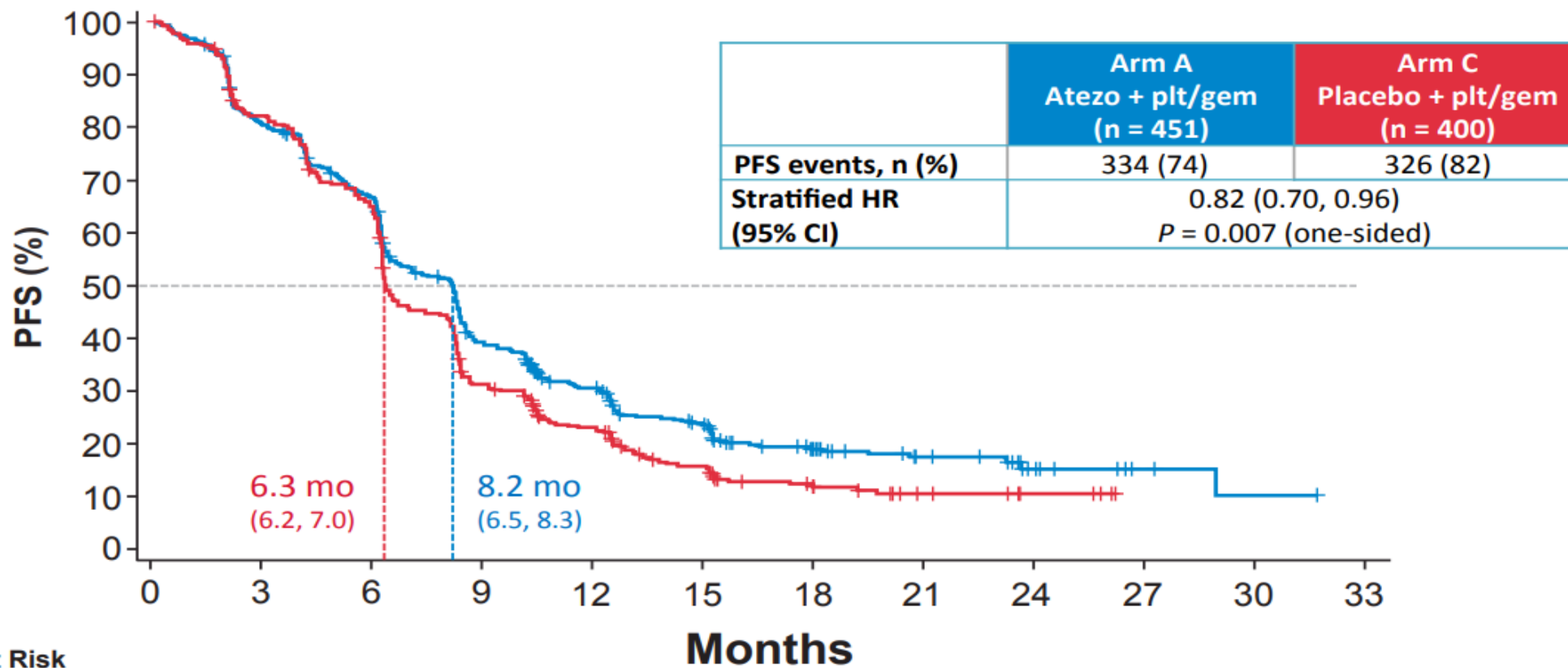


- **Coprimary endpoints:** investigator-assessed PFS and OS (Arm A vs C); OS (Arm B vs C; hierarchical approach)
- **Key secondary endpoints:** INV-ORR and DoR, PFS and OS (arm B vs C; PD-L1 IC2/3 subgroup), and safety

* Including KPS <80% vs ≥80% and presence of visceral metastases.

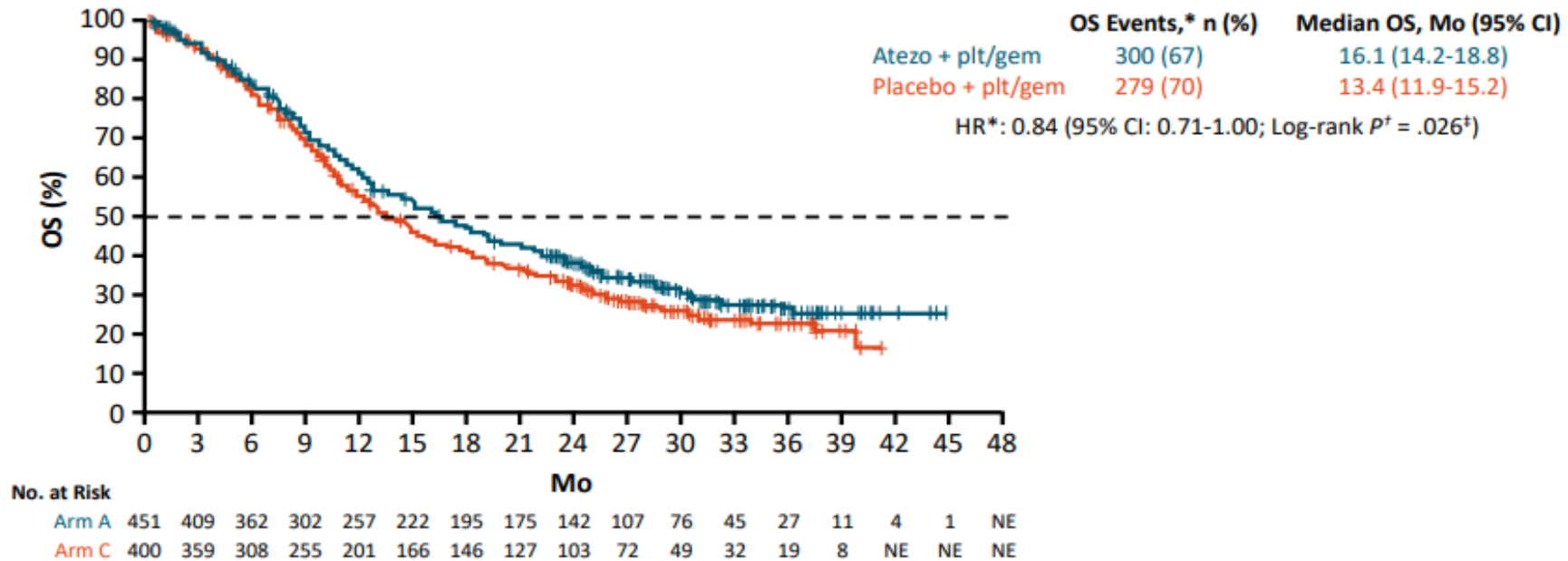


Final PFS: ITT (Arm A vs Arm C)



NE, not estimable. Data cutoff 31 May 2019; median follow-up 11.8 months.

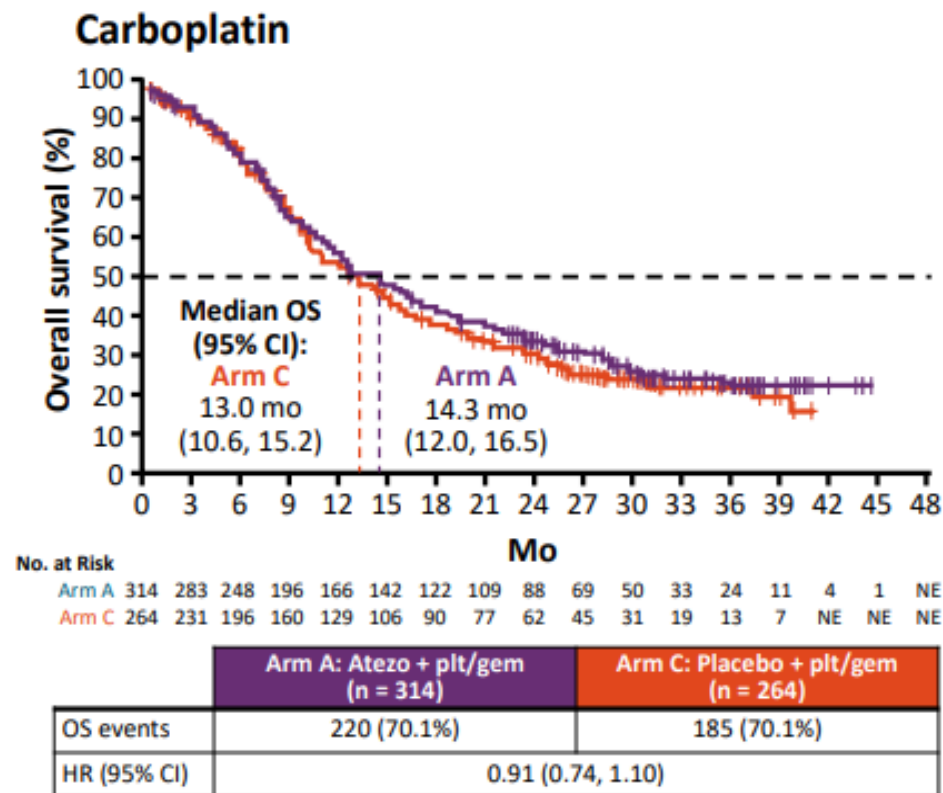
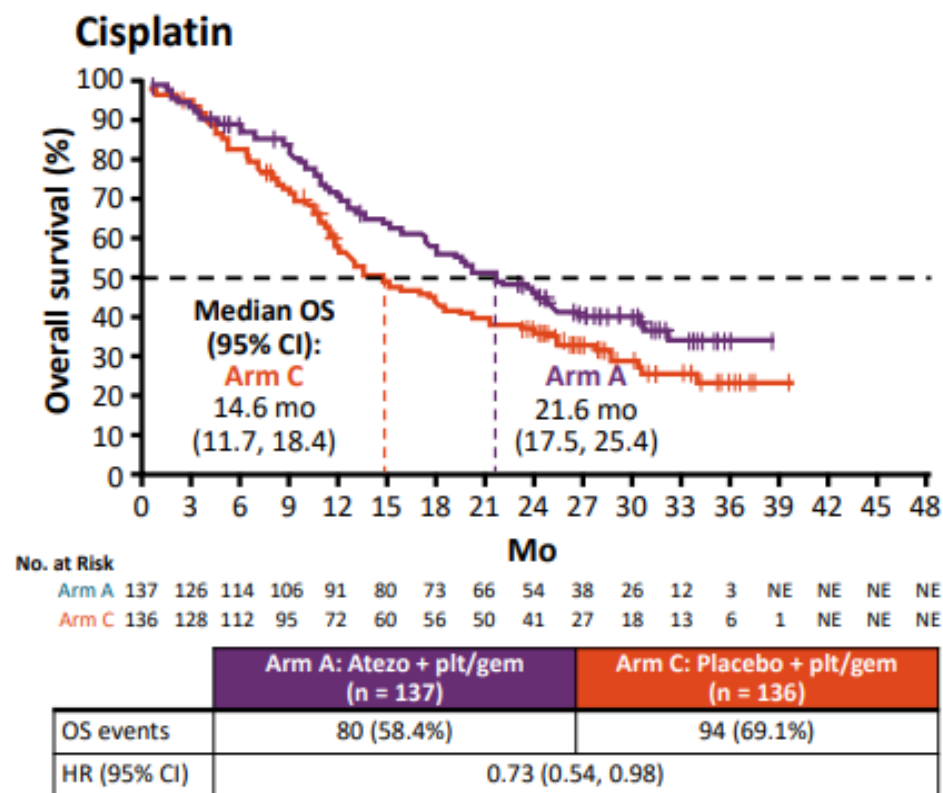
IMvigor130: OS (Co-Primary Endpoint) With PlatinumBased Chemotherapy ± Atezolizumab in Advanced



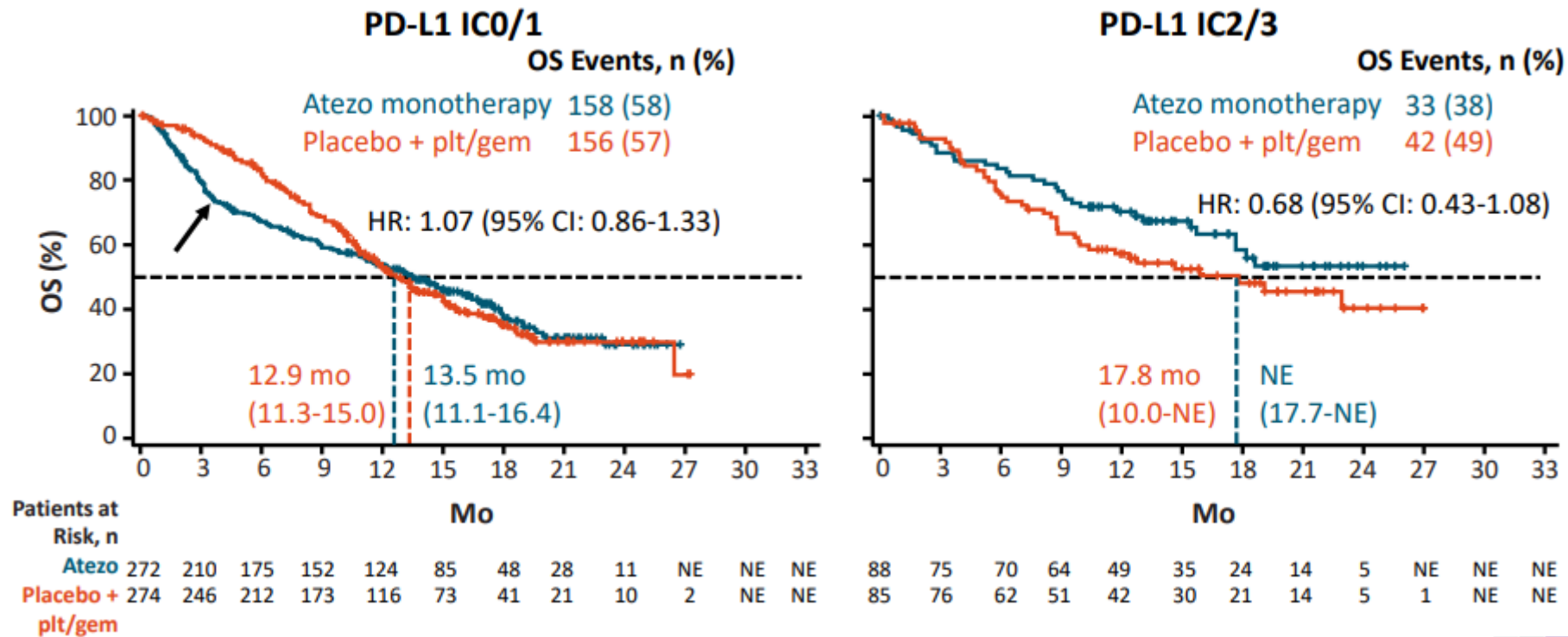
* Stratified by PD-L1 status, Bajorin risk factors and/or liver metastases, investigator's choice of plt/gem, and enrollment stage.

[†] P value is 1-sided. [‡] Not statistically significant (interim efficacy boundary 0.014, 1-sided).

IMvigor130: OS by Choice of Chemotherapy



IMvigor130: Interim OS (Atezolizumab vs Platinum Chemotherapy) by PD-L1 Status

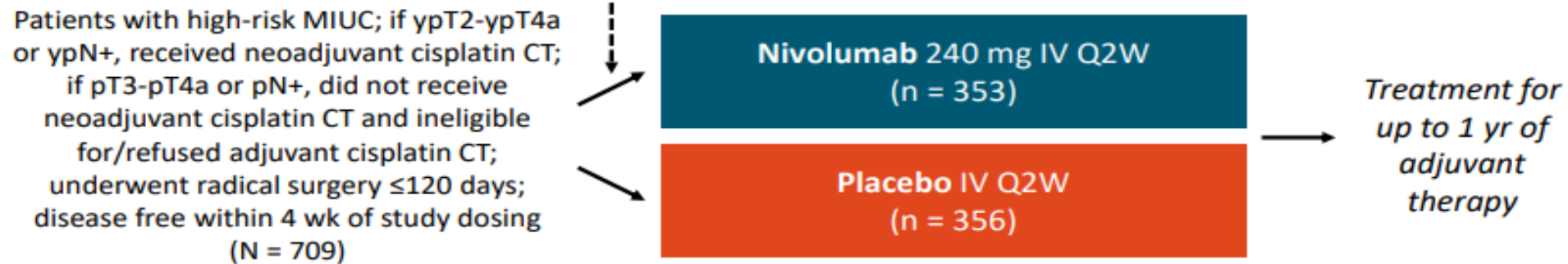


Adjuvant Therapy in High-Risk MIUC

CheckMate 274: Adjuvant Nivolumab vs Placebo After Radical Surgery

- First analysis of international, randomized, double-blind phase III trial

Stratified by PD-L1 status (< vs ≥1%), previous neoadjuvant cisplatin-based CT, nodal status*



- **Primary endpoints:** DFS is ITT population, DFS in all randomized patients with PD-L1 ≥1%

* Per PD-L1 IHC 28-8 PharmDx assay.

† OS data immature at time of analysis.

- **Secondary endpoints:** nonurothelial tract recurrence-free survival, disease-specific survival, OS[†]

- **Exploratory endpoints:** distant metastasis-free survival, safety, HRQoL

CheckMate 274: Baseline Characteristics, Patient Disposition

Parameter	Nivolumab	Placebo
Characteristic	n = 353	n = 356
Mean age, yr (range)	65.3 (30-92)	65.9 (42-88)
Male, %	75.1	77.2
ECOG PS, %		
▪ 0	63.5	62.1
▪ 1	34.6	35.1
▪ 2	2.0	2.5
Tumor origin		
▪ Urinary bladder	79.0	78.9
▪ Renal pelvis	12.5	14.6
▪ Ureter	8.5	6.5
Time from diagnosis to randomization		
▪ <1yr	92.1	91.0
▪ ≥1yr	7.9	9.0
PD-L1 ≥1%	39.7	39.9
Previous neoadjuvant cisplatin	43.3	43.5

Parameter, %	Nivolumab	Placebo
Characteristic	n = 353	n = 356
Pathologic T stage at resection		
▪ pT0-2	23.8	25
▪ pT3	58.4	57.3
▪ pT4a	16.1	17.4
▪ Not reported	0.3	0.3
Nodal status at resection		
▪ pT2N-	7.1	8.1
▪ pT3, 4N-	44.8	44.7
▪ pT0-4N1	20.1	20.2
▪ pT0-4N2,3	27.2	27.0
▪ pTisN-	0.3	0
▪ Not reported	0.6	0
Disposition	n = 351	n = 348
Discontinued treatment	53.3	56.3

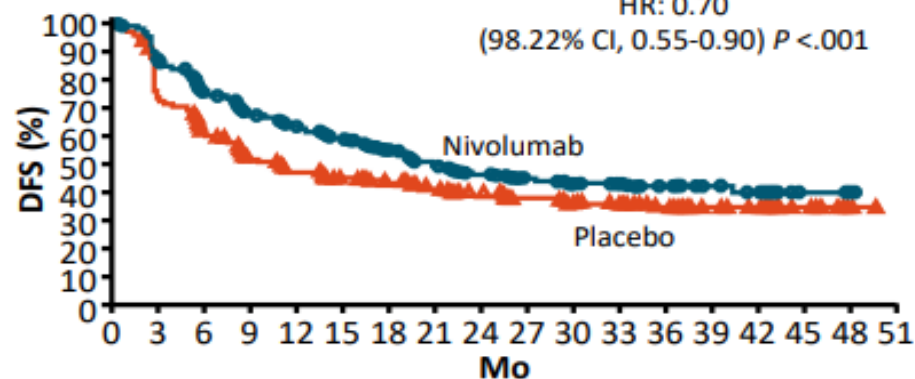
- With nivolumab vs placebo, fewer d/c due to disease recurrence (25.6% vs 42.2%), more d/c due to study drug toxicity (14.0% vs 2.3%)

CheckMate 274: DFS

DFS in ITT (Coprimary Endpoint)

	No. of Events/ No. of Patients	DFS at 12 Mo (95% CI)
Nivolumab	170/353	62.8 (57.3–67.8)
Placebo	204/356	46.6 (41.1–51.9)

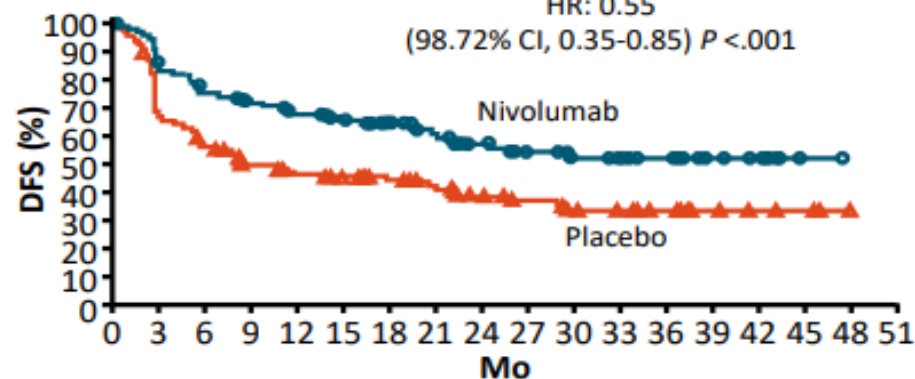
HR: 0.70
(98.22% CI, 0.55-0.90) $P < .001$



DFS in Patients With PD-L1 $\geq 1\%$ (Coprimary Endpoint)

	No. of Events/ No. of Patients	DFS at 12 Mo (95% CI)
Nivolumab	55/140	67.2 (58.4-74.5)
Placebo	81/142	45.9 (37.1-54.2)

HR: 0.55
(98.72% CI, 0.35-0.85) $P < .001$



- Nivolumab prolonged DFS vs placebo in most subgroups of ITT population except for patients with initial tumor origin in renal pelvis (HR: 1.23; 95% CI: 0.67-2.23) and ureter (HR: 1.56; 95% CI: 0.70-3.48)

CheckMate 274: Safety and HRQoL

Safety Outcome, %	Nivolumab		Placebo	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3
Outcome	n = 351		n = 348	
Any-cause AE	98.9	42.7	95.4	36.8
TRAE	77.5	17.9	55.5	7.2
TRAE in ≥5% of Patients*				
Pruritus	23.1	0	11.5	0
Fatigue	17.4	0.3	12.1	0
Diarrhea	16.8	0.9	10.9	0.3
Rash	15.1	0.6	5.5	0
Lipase increase	9.7	5.1	5.7	2.6
Hypothyroidism	9.7	0	1.4	0
Amylase increase	9.4	3.7	5.7	1.4
Hyperthyroidism	9.4	0	0.9	0

Select TRAE With Potential Inflammatory Mechanism	Nivolumab (n = 351)		Placebo (n = 348)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3
Skin	40.7	1.7	17.8	0
Endocrine	19.1	0.3	3.7	0
Gastrointestinal	18.5	1.7	11.2	0.9
Hepatic	8.3	1.7	4.9	0.3
Renal	7.1	1.1	3.4	0
Pulmonary	5.4	1.4	1.4	0

- Most common Gr ≥3 select TRAEs with nivolumab: 0.9% each for diarrhea, colitis, pneumonitis; with placebo, colitis (0.6%); 0.3% each for diarrhea, GGT increase, hepatitis
- No HRQoL deterioration with nivolumab vs placebo
- 2 deaths due to pneumonitis in the nivolumab arm

* Also included asthenia, nausea, decreased appetite, blood creatinine increase, and maculopapular rash.



0.93; $P = .014$). Based on these results, ddMVAC is preferred over GC for adjuvant chemotherapy.

Checkpoint inhibitors have also been investigated in the adjuvant setting, with the phase 3 CheckMate 274 trial of adjuvant nivolumab reporting positive results for its primary endpoints across the entire study population, although the authors note the possibility of a larger effect size for bladder compared to UTUC (see *Adjuvant Treatment and Follow-up under UTUC*, below for more discussion on these data).¹⁷⁶ In the ITT population of 709 patients with muscle invasive urothelial carcinoma treated with radical surgery on CheckMate 274, DFS was 20.8 months with nivolumab compared to 10.8 months with placebo (HR, 0.70; 98.22% CI, 0.55–0.90; $P < .001$). For patients with a programmed death-ligand 1 (PD-L1) expression level of 1% or more, DFS was 74.5% with nivolumab and 55.7% with placebo (HR, 0.55; 98.72% CI, 0.35–0.85; $P < .001$). Importantly, adjuvant nivolumab was tested both in patients who had received neoadjuvant therapy as well as those who did not; 43.4% of the trial participants had received previous cisplatin-based neoadjuvant therapy. Treatment-related AEs of grade 3 or higher occurred in 17.9% of those treated with nivolumab and 7.2% of placebo. Further follow-up is ongoing to assess OS outcomes. While atezolizumab has also been tested in the adjuvant setting for patients with high-risk muscle invasive urothelial carcinoma in the phase 3 IMvigor010 study, this study failed to meet its primary endpoint of improved DFS with adjuvant atezolizumab compared to observation.¹⁷⁷ Median DFS was 19.4 months with atezolizumab compared to 16.6 months with observation (HR, 0.89; 95% CI, 0.74–1.08; $P = .24$).

The NCCN Guidelines suggest that adjuvant systemic therapy should be discussed with patients with high-risk pathology after cystectomy. If cisplatin-based neoadjuvant therapy was not given and the tumor is

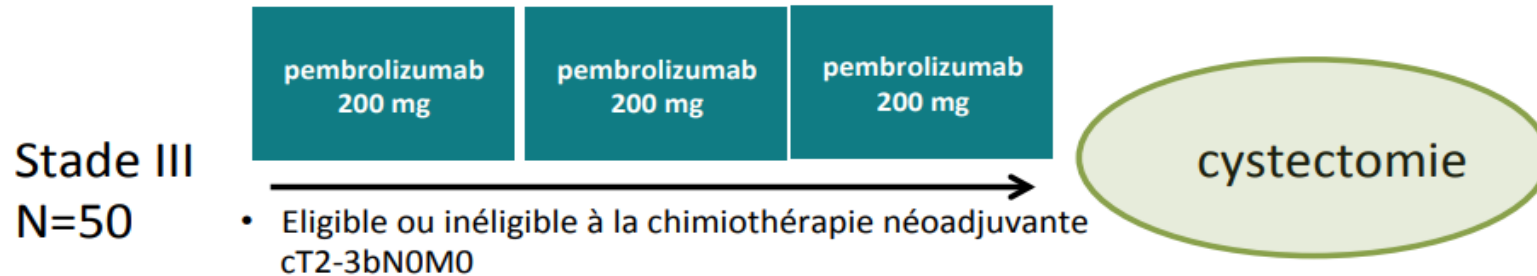
found to be pT3, pT4, or pN+ following resection, adjuvant cisplatin-based chemotherapy is the preferred approach, although adjuvant nivolumab may also be considered. If cisplatin-based neoadjuvant therapy was given and the tumor is ypT2–ypT4a or ypN+, nivolumab may be considered, although consideration of this approach should balance its effect at delaying progression of disease with the risk of side effects. A minimum of 3 cycles of a cisplatin-based combination, such as ddMVAC (preferred) or GC, may be used in patients undergoing perioperative chemotherapy. Chemotherapy regimen and dosing recommendations are mainly based on studies in advanced disease.^{145,157,178,179} Carboplatin has not demonstrated a survival benefit and should not be substituted for cisplatin in the perioperative setting. It should be noted that patients with tumors that are pT2 or less and have no nodal involvement or lymphovascular invasion after cystectomy are considered to have lower risk and are not recommended to receive adjuvant therapy.

Adjuvant Radiation

Patients with locally advanced disease (pT3–4) have high rates of pelvic recurrence and poor OS after radical cystectomy, PLND, and perioperative chemotherapy (pelvic failure 20%–45% and survival 10%–50% at 5 years, depending on risk factors).^{180–183} There is an interest in using adjuvant radiation to improve these outcomes, but data are limited and further prospective studies are needed to confirm its benefits. One older randomized study of 236 patients with pT3a to pT4a bladder cancer demonstrated improvement in 5-year DFS and local control compared to surgery alone.¹⁸⁴ A more recent randomized phase II trial compared adjuvant sequential chemotherapy and radiation versus adjuvant chemotherapy alone in 120 patients with locally advanced disease with one or more risk factors (\geq pT3b, grade 3, or node-positive), in a study population with a high proportion of squamous cell carcinoma. This study demonstrated a significant improvement in local

Place de L'immunothérapie en néoadjuvant

PURE-01: pembro est-il actif ? Quels biomarqueurs (ADN, RNA, PDL1) ?

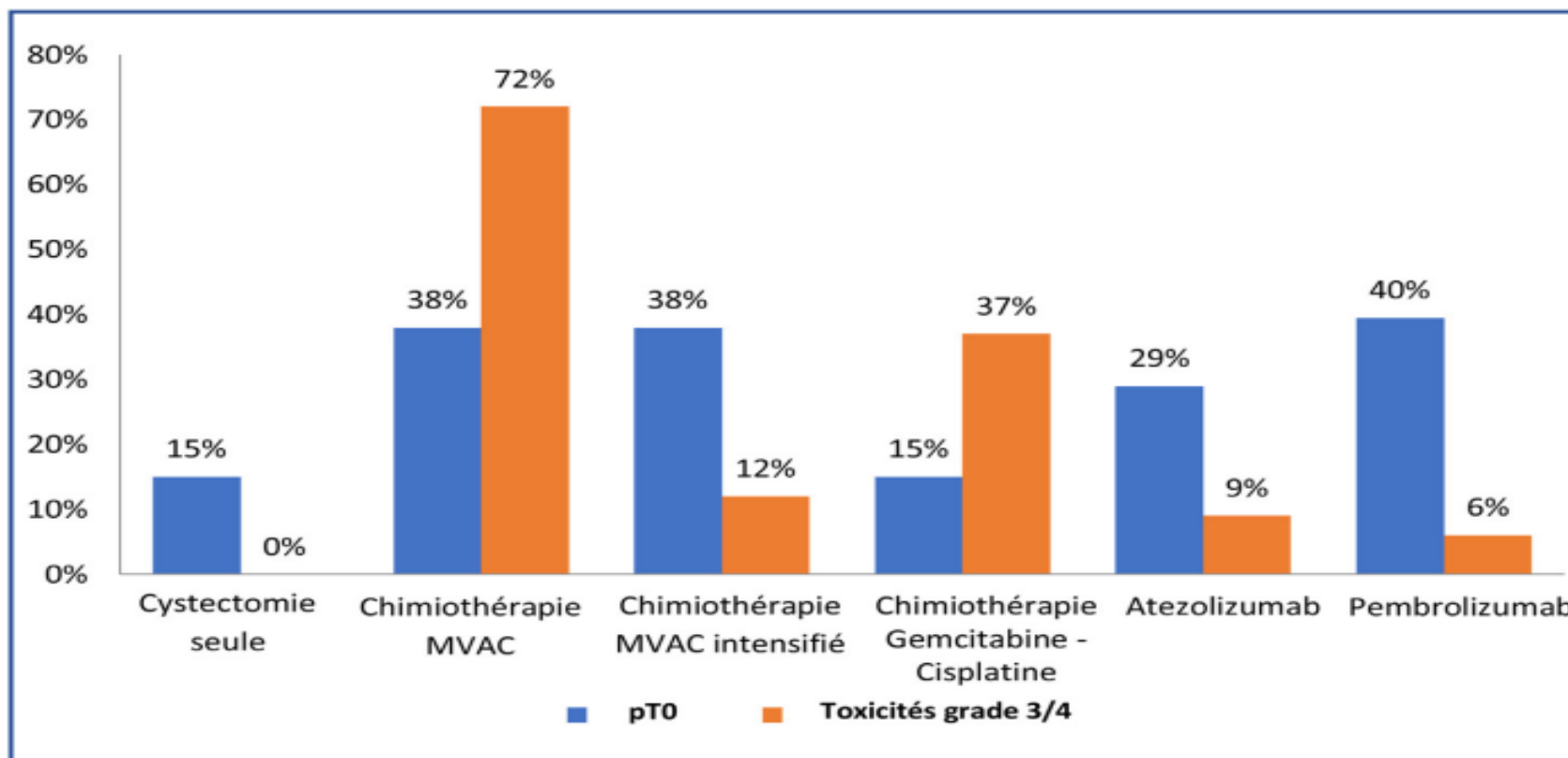


- Tous les patients ont été opérés (96% dans les 12 semaines)
- 94% ont eu les trois cycles
- 30% de complications opératoires (sepsis, occlusion)
- Grade $\frac{3}{4}$: 6%

pCR= 42%
pCR = 54% si PDL1+

Expression PDL1 - Charge mutationnelle- Signature inflammatoire
Associées avec la réponse

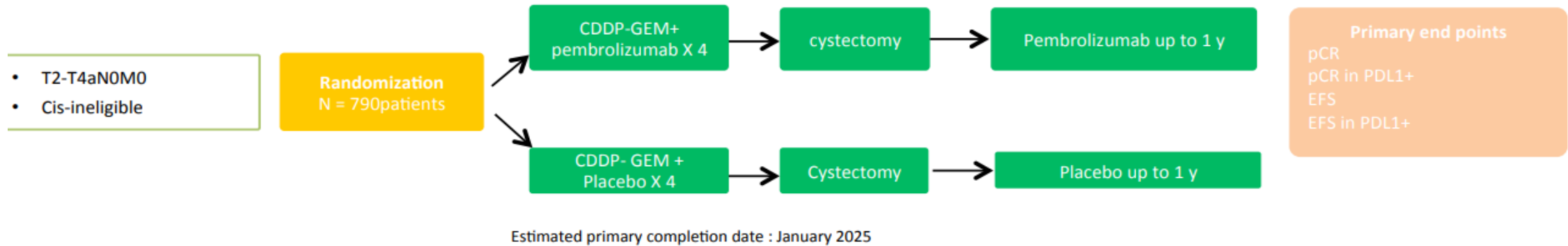
Réponse pathologique - Toxicités



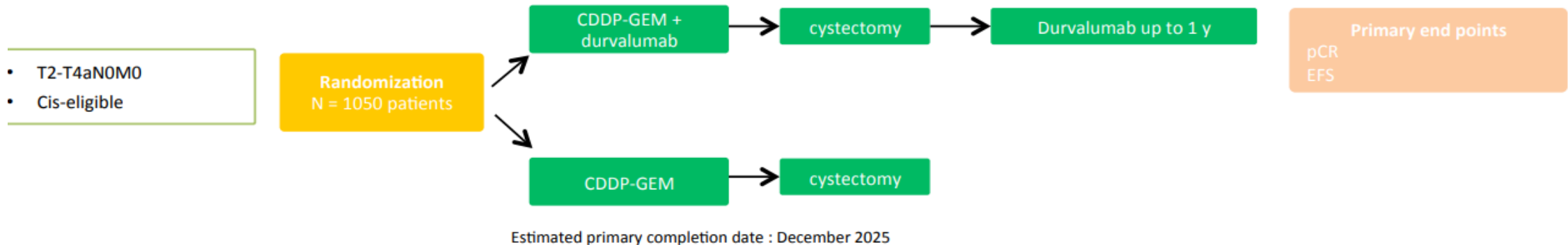
Taux de réponse pathologique complète (pT0) et toxicités (grade 3/4) des différentes stratégies néoadjuvantes avant cystectomie.

Les essais de combinaison néo-adjuvante de phase 3 en cours

KEYNOTE 866 Study Design (NCT03924856)



NIAGARA Study Design (NCT03732677)

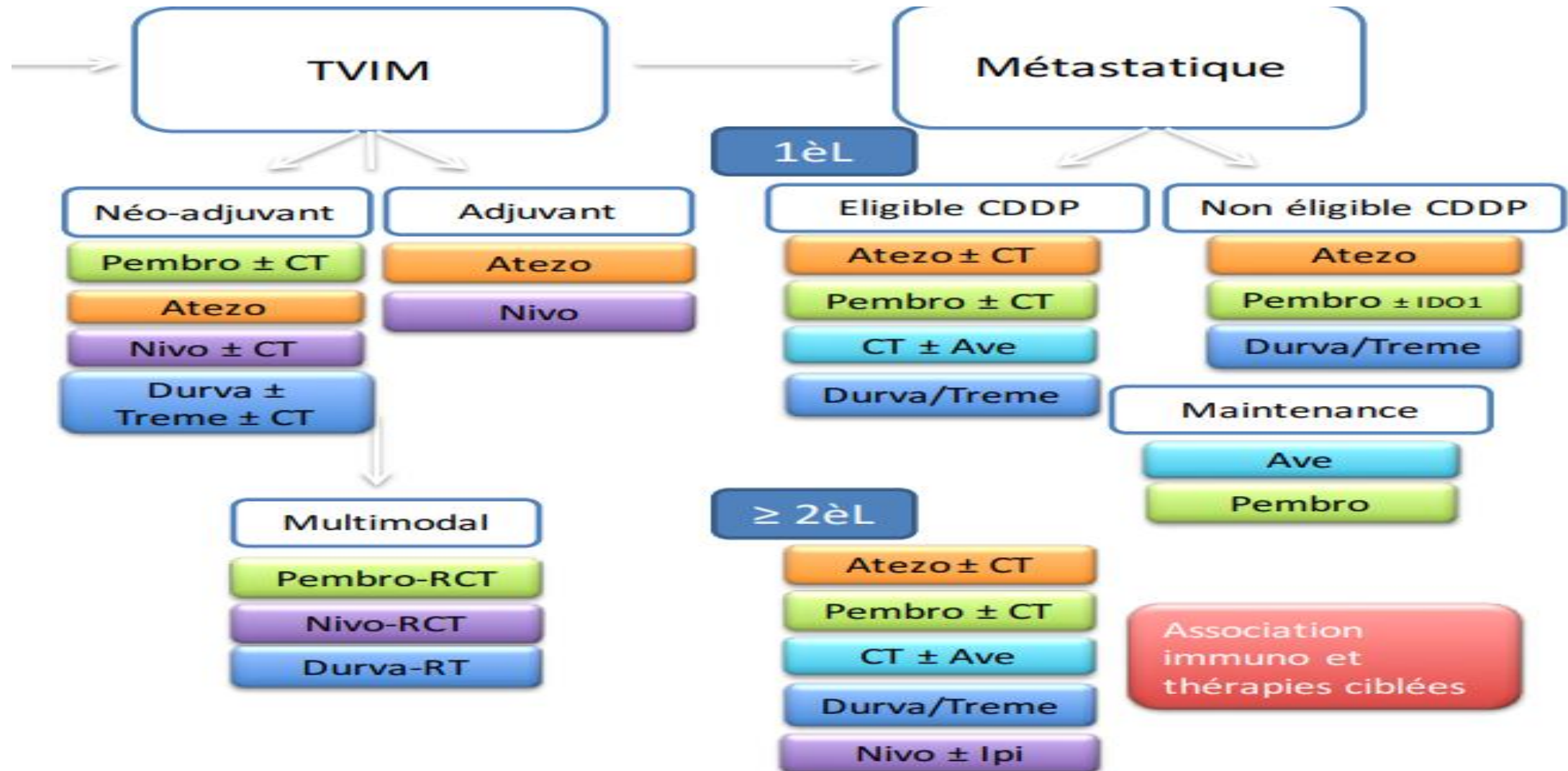


Alternatives à la cystectomie : de nouvelles pistes

Chimio-Immunothérapie (Pembro-Gem) ou combinaison d'immunothérapie (Durva-Treme)+ Radiothérapie dans le cancer de vessie infiltrant le muscle, en vue d'une préservation d'organe.

Critères	Étude 4504	Etude 4505
Phase	2	2
Stade	cT2-T4aN0MO	cT2-T4aN0MO
Critères inclusion	Refus ou inéligible cystectomie, PS0/1, DFG>30 mL/min, Pas de CI RT pelvis ou pembro pas de CT pré op	PS0/1, pas CI IT, voulant préservation ou inéligible cystectomie
Traitement	Pembro 1 cure, 2-3 semaines après RTUV puis RT (52Gy/20fx) + Gemcitabine 27mg/m ² 2 fois par semaine + Pembro/3sem	RTUV puis 3 cycles/4sem Durva 1,5g-Treme 75mg, RT 46Gy pelvis et 64-66Gy vessie 2sem après C1 IO/IO. Si maladie résiduelle proposition de cystectomie
Objectifs	SSM avec vessie intacte à 2 ans	Réponse complète (abs MIBC biopsie post traitement)
Nombre de patients inclus	6 pour cohorte sécurité (CS) + 48 pour cohorte efficacité (CE)	32
Médiane d'âge	67 (CS) et 74 (CE)	71
Stade	74% cT2, 22% cT3, 4% cT4	87% cT2, 9,3% cT3, 3,1% cT4
Résultats	0 récurrence CS; 25% récurrence CE; Taux RC 100% SSM à 1 an = 77% CS et 83% CE	Taux RC 81%, A 6 mois SSM vessie intacte 76%, SSM globale 80%, SG 93%
Effets indésirables	EI G3 35%	EI G3 31%

Immunothérapie : panorama dans le carcinome urothélial



Recherche de nouveaux biomarqueurs

- L'immunothérapie est donc devenue un traitement standard dans le CU avancé.
- Trouver de nouvelles combinaisons, de nouvelles stratégies, ...et des biomarqueurs efficaces dans la prédiction d'une réponse (ou non réponse) aux ICIs.
- l'expression PD-L1 est dynamique et évolue avec le temps et les traitements administrés.

Recherche de nouveaux biomarqueurs

- Les critères de positivité de l'expression PD-L1 sont différents en raison d'un manque de standardisation.
- Récemment, le Tumor Cancer Genome Atlas (TCGA) a identifié deux sous-ensembles moléculaires de CU (Cluster III et Cluster II) qui sont associés à une meilleure sensibilité aux ICIs, suggérant d'incorporer la signature moléculaire dans cette quête de biomarqueurs.

Conclusion

- L'immunothérapie fait à présent partie de l'arsenal des oncologues pour le traitement du cancer de la vessie par le blocage des points de contrôle tel que l'axe PD1-PDL1.
- Elles ont montré un intérêt dans le cancer urothélial , en permettant une amélioration significative de la survie globale aux stades métastatiques.
- L'identification de marqueurs prédictifs de la réponse à l'immunothérapie est désormais indispensable pour optimiser la prise en charge et guider la prescription rationalisée de ces nouvelles molécules coûteuses , selon le concept de pharmacogénomique.