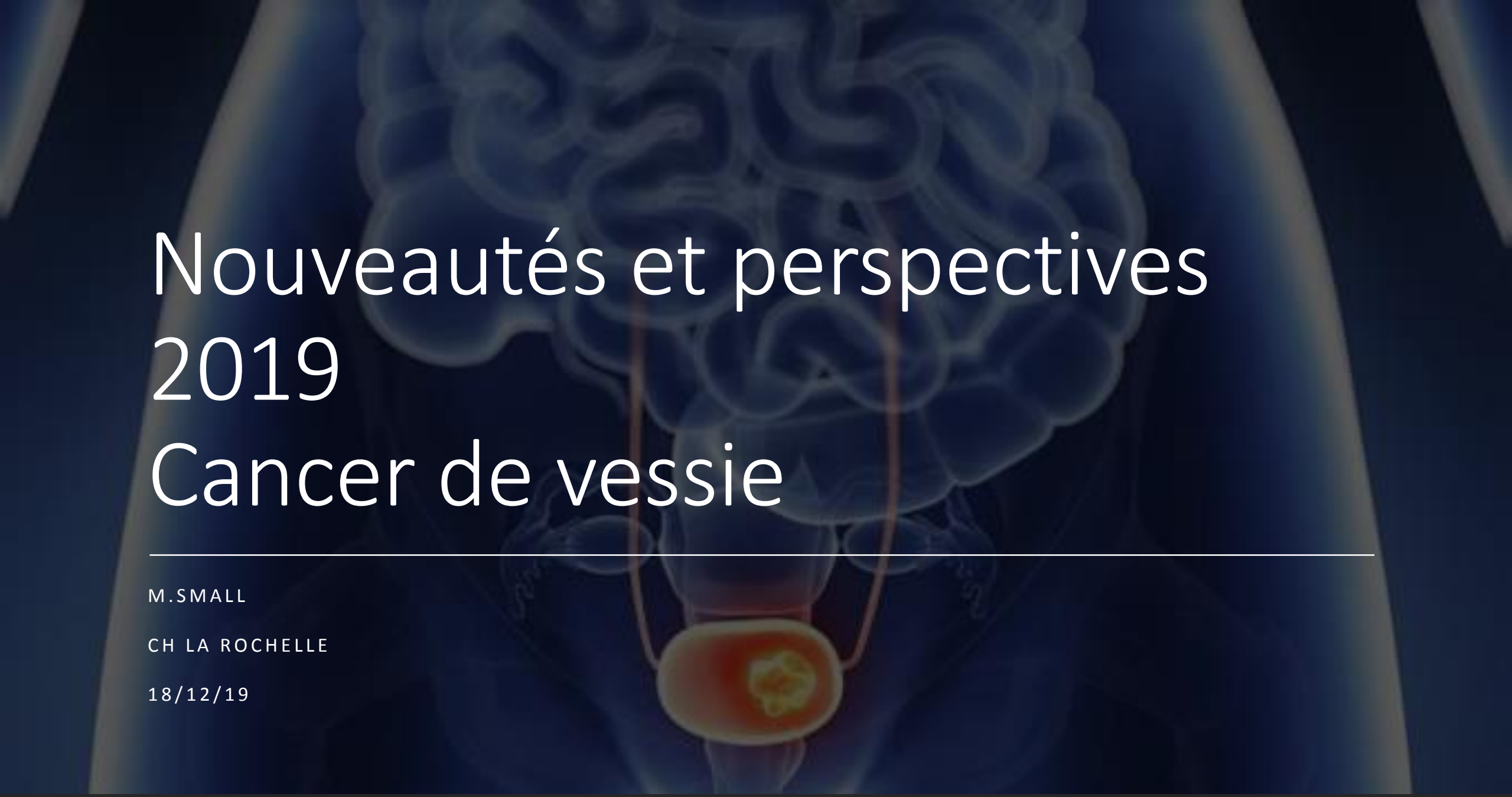


Nouveautés et perspectives 2019
Cancer de vessie

M.SMALL

CH LA ROCHELLE

18/12/19

Contexte

01

Métastatique : pronostic sombre, peu d'options thérapeutiques

02

TVIM : potentiellement létale et délabrante

03

TVNIM : potentielle TVIM

Contexte

01

Métastatique : pronostic sombre, peu d'options thérapeutiques

Peut-on améliorer le pronostic ?

02

TVIM : potentiellement létale et délabrante

Peut-on améliorer le pronostic ? Préservation d'organe ?

03

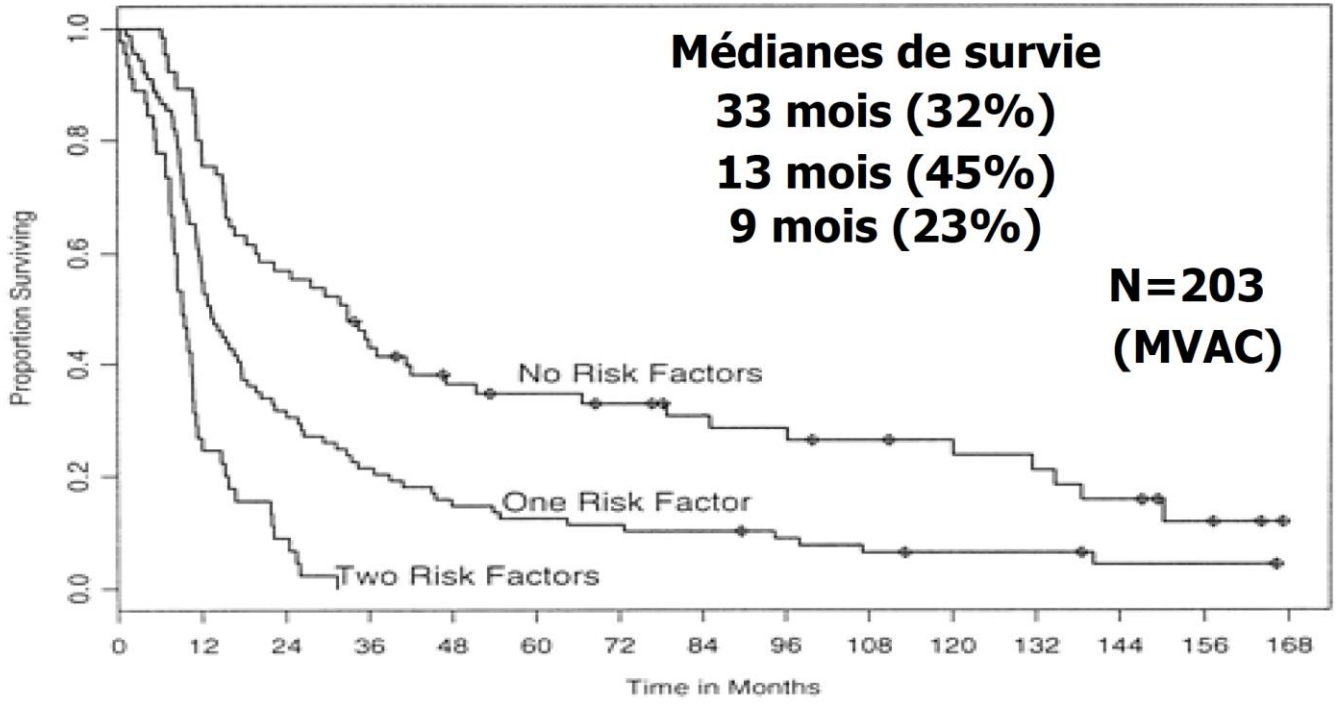
TVNIM : potentielle TVIM

Peut-on faire mieux que le BCG ?

Vessie métastatique : étayer l'arsenal thérapeutique

Pronostic sombre

50 % des patients unfit pour le cisplatine



Vessie métastatique : étayer l'arsenal thérapeutique

Première ligne

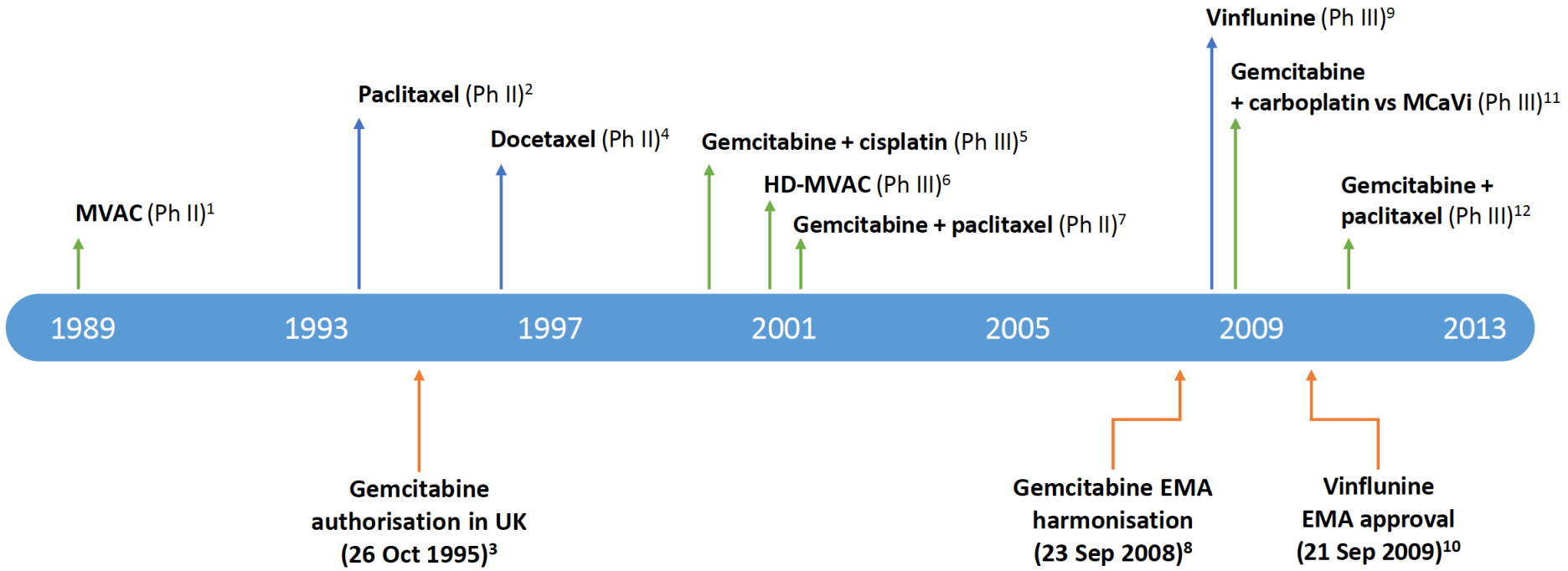
	CHIMIOTHERAPIE Avec le cisplatine	CHIMIOTHERAPIE Avec le carboplatine
Taux de réponse	50%	35%
PFS médiane	7 mois	4 mois
OS médiane	13 mois	9 mois

Deuxième ligne

Pas de standard

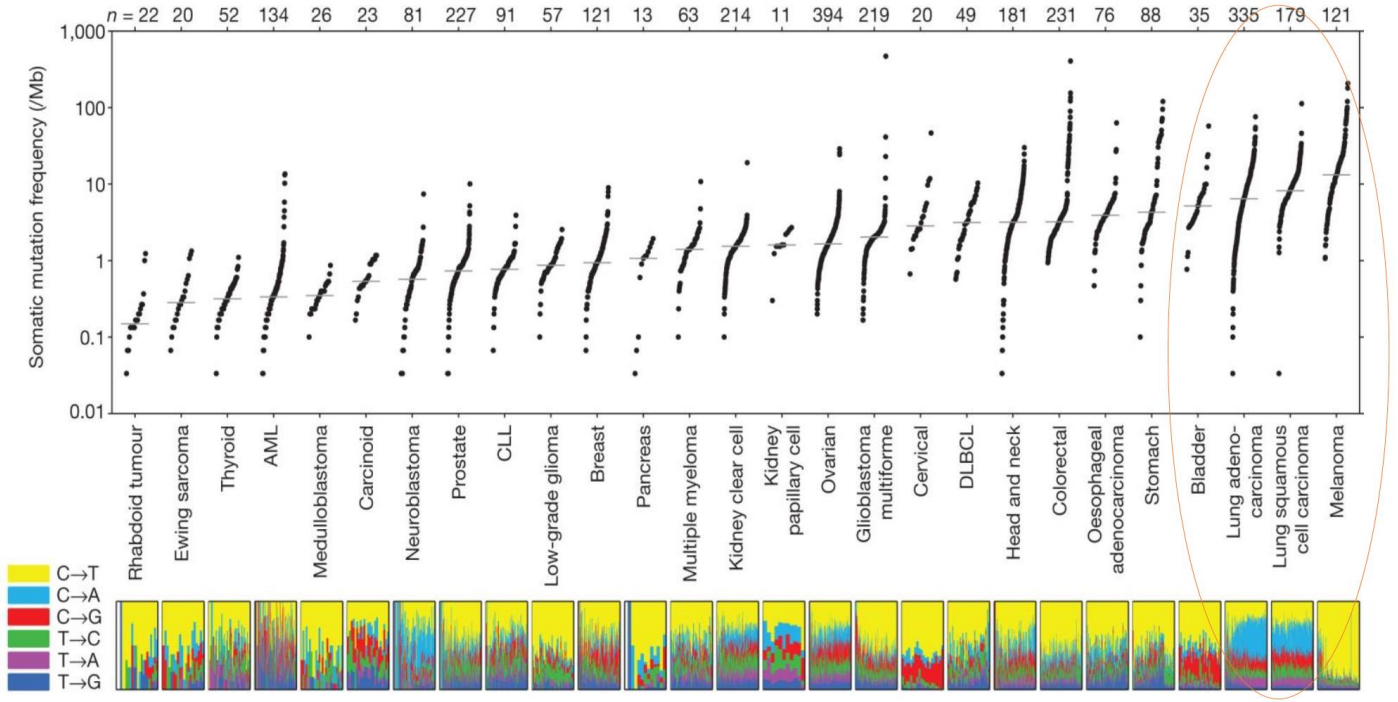
Vinflunine, paclitaxel…

Vessie métastatique : étayer l'arsenal thérapeutique



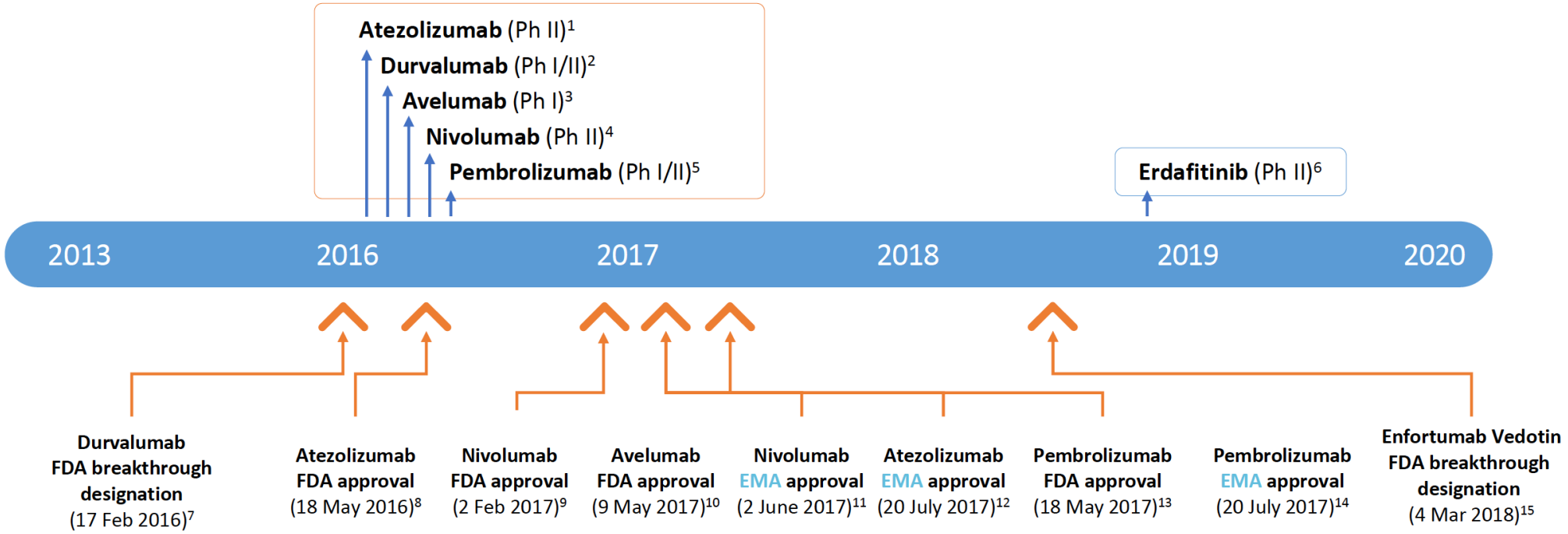
1. Sternberg CN, et al. Cancer 1989;64:2448–2458; 2. Roth BJ, et al. J Clin Oncol 1994;12:2264–2270; 3. Eli Lilly. SmPC Gemzar® 01 Jul 2014. Available at: www.medicines.org.uk;
4. McCaffrey JA, et al. J Clin Oncol 1997;15:1853–1857; 5. Von der Maase H, et al. J Clin Oncol 2000;18:3068–3077; 6. Sternberg CN, et al. J Clin Oncol 2001;19:2638–2646;
7. Meluch AA, et al. J Clin Oncol 2001;19:3018–3024; 8. EMA. EMEA/CHMP/512295/2008; 24 Sept 2008. Available at: www.ema.europa.eu; 9. Bellmunt J et al. J Clin Oncol 2009;2:4454–4461;
10. EMA. EMEA/H/C/000983; 2012. Available at: www.ema.europa.eu; 11. De Santis M et al. J Clin Oncol 2009;27:5634–5639; 12. Bellmunt J et al. J Clin Oncol 2012;30:1107–1113.

Charge mutationnelle par cancer



Lawrence MS, et al. Nature 2013;499:214–218.

Vessie métastatique : étayer l'arsenal thérapeutique



1. Rosenberg JE et al. Lancet 2016;387:1909–1920; 2. Powells T, et al. JAMA Oncol 2017;3(9):e172411; 3. Patel MR, et al. Lancet Oncol 2018;19:51-64; 4. Sharma P, et al. Lancet Oncol 2017;18:312–322; 5. Woodcock VK, et al. ASCO 2016 (Abstract No. 406); 6. Loriot Y, et al. N Engl J Med 2019;381:338–348; 7. AstraZeneca. Press release 17 Feb 2016. Available at: www.astrazeneca.com; 8. FDA. Press release 18 May 2016. Available at: www.fda.gov; 9. FDA. Press release 2 Feb 2017. Available at: www.fda.gov; 12. FDA. Press release 9 May 2017. Available at www.fda.gov; 10. EMA. www.ema.europa.eu/en/documents/variation-report/opdivo-h-c-3985-ii-0041-epar-assessment-report-variation_en.pdf; 11. EMA. https://www.ema.europa.eu/en/documents/assessment-report/tecentriq-epar-public-assessment-report_en.pdf; 13. FDA. Press release 18 May 2017. Available at www.fda.gov; 14. EMA. www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-keytruda_en.pdf; 15. FDA. Press release 4 March 2018. Available at: www.fda.gov.

Vessie métastatique après cisplatine

	Atezolizumab[1,2]	Nivolumab[3]	Pembrolizumab[4]	Avelumab[5,6]	Durvalumab[7]
Phase	Phase II single arm[1]/ Phase III randomized[2] (IMvigor 210/211)	Phase II single arm (CheckMate 275)	Phase III randomized (KEYNOTE-045)	Phase Ib (JAVELIN Solid Tumor)	Phase I/II (NCT01693562)
Number of patients	310[1]/467[2]	265	270	249[5] 44[6]	191
Dosing	1200 mg q3w[1,2]	3 mg/kg q2w	200 mg q3w	10 mg/kg q2w	10 mg/kg q2w
ORR	15%; IC2/3 26%[1] / 13.4%; IC2/3 23%[2]	19.6%	21.1%	17%[5] 18.2%[6]	17.8%
Duration of response	84% ongoing at median follow-up of 11.7 months[1]/ 15.9 months[2]	77% ongoing at median follow-up of 7.0 months	72% ongoing at median follow-up of 14.1 months	82% ongoing at data cutoff[5]/ 75% ongoing at data cutoff[6]	Not reached at data cut
Median OS	7.9[1]/11.1[2] months	8.7 months	10.3 months	6.5[5]/13.7[6] months	18.2 months
Median PFS	2.1 months[1]/NR[2]	2.0 months	2.1 months	6.3[5]/11.6 weeks[6]	1.5 months
Grade 3/4 TRAEs	16%[1]/20%[2]	18%	15% (G3–5)	8% (≥G3)[5]/6.8%[6]	6.8%

1. Rosenberg JE, et al. Lancet 2016;387:1909–1920; 2. Powles T, et al. Lancet 2018;391:748-57; 3. Sharma P, et al. Lancet Oncol 2017;18:312–322; 4. Bellmunt J, et al. N Engl J Med 2017 2017;376:1015–1026; 5. Patel MR, et al. Lancet Oncol 2018;19:51–64; 6. Apolo AB, et al. J Clin Oncol 2017;35:2117–2124; 7. Powles T, et al. JAMA Oncol. doi:10.1001/jamaoncol.2017.2411.

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	Atezolizumab[1,2]	Nivolumab[3]	Pembrolizumab[4]	Avelumab[5,6]	Durvalumab[7]
Phase	Phase II single arm[1]/ Phase III randomized[2] (IMvigor 210/211)	Phase II single arm (CheckMate 275)	Phase III randomized (KEYNOTE-045)	Phase Ib (JAVELIN Solid Tumor)	Phase I/II (NCT01693562)
Number of patients	NON REMBOURSE	NON REMBOURSE	REMBOURSE	NON REMBOURSE	NON REMBOURSE
Dosing	1200 mg q3w[1,2]	3 mg/kg q2w	200 mg q3w	10 mg/kg q2w	10 mg/kg q2w
ORR	15%; IC2/3 26%[1] / 13.4%; IC2/3 23%[2]	19.6%	21.1%	17%[5] 18.2%[6]	17.8%
Duration of response	84% ongoing at median follow-up of 11.7 months[1]/ 15.9 months[2]	77% ongoing at median follow-up of 7.0 months	72% ongoing at median follow-up of 14.1 months	82% ongoing at data cutoff[5]/ 75% ongoing at data cutoff[6]	Not reached at data cut
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Vessie métastatique non éligible au cisplatine

	Atezolizumab[1]	Pembrolizumab[2,3]
Phase	Phase II (IMvigor Cohort 1)	Phase II (KEYNOTE-052)
Number of patients	119	370
Dosing	1200 mg every 3 weeks	200 mg every 3 weeks
ORR	23% (9% CR)	29% (7% CR)
Duration of response	70% of responses ongoing at 17.2 months	82% of responses ongoing at ≥6 months
Median OS	15.9 months	11.5 months[3]
Median PFS	2.7 months	2.0 months
Rate of Grade 3/4 treatment-related AEs	16%	19%

For cisplatin-ineligible patients, indication for both agents is restricted to PD-L1 expressing tumors

1. Balar AV, et al. Lancet 2017;389:67–76; 2. O'Donnell PH, et al. ASCO 2017 (Abstract No. 4502); 3. Vuky J, et al. ASCO 2018 (Abstract No. 4524).

Vessie métastatique non éligible au cisplatine

	Atezolizumab[1]	Pembrolizumab[2,3]
Phase	Phase II (IMvigor Cohort 1)	Phase II (KEYNOTE-052)
Number of patients	119	370
Dosing	1200 mg every 3 weeks	mg every 3 weeks
ORR	23% (9% CR)	29% (7% CR)
Duration of response	70% of responses at 17.2 month	82% of responses ongoing at ≥6 months
Median OS	15.9 months	11.5 months[3]
Median PFS	2.7 months	2.0 months
Rate of Grade 3/4 treatment-related AEs	16%	19%

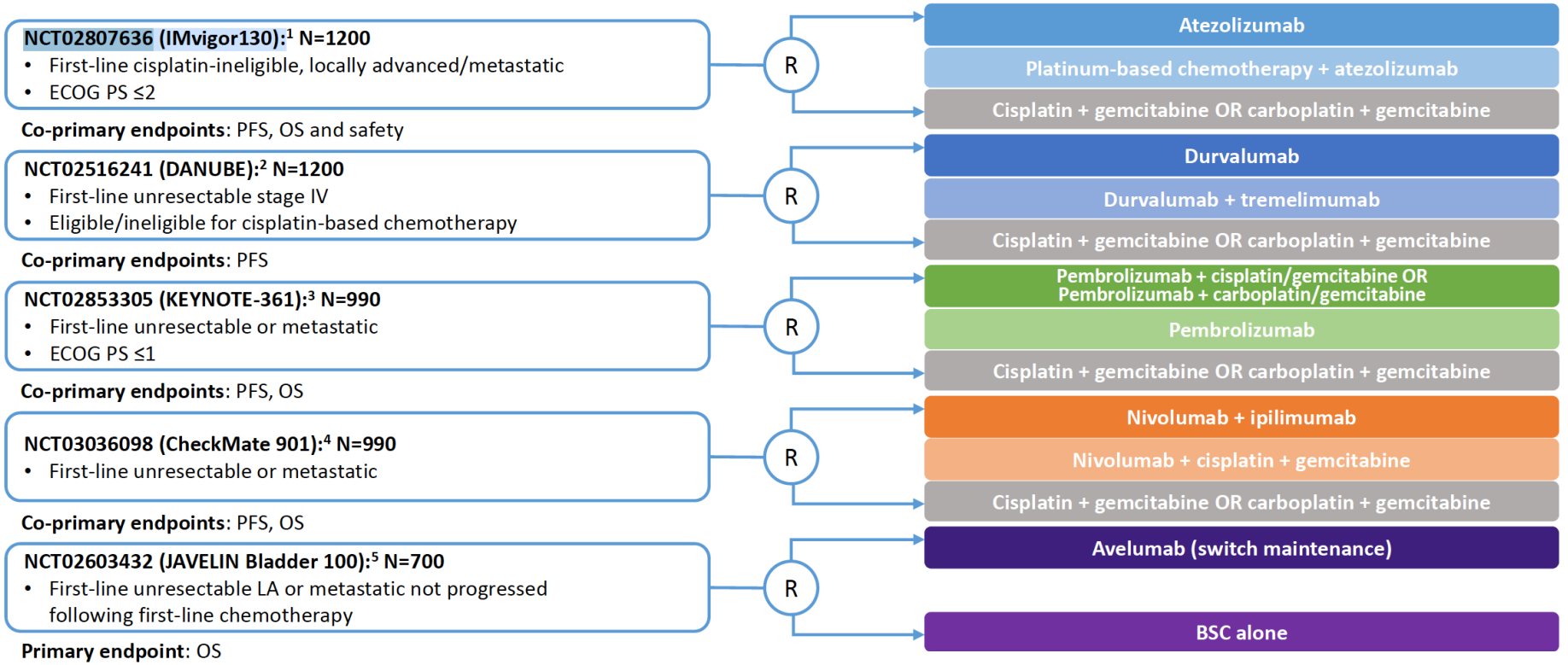
NON REMBOURSE

For cisplatin-ineligible patients, indication for both agents is restricted to PD-L1 expressing tumors

1. Balar AV, et al. Lancet 2017;389:67–76; 2. O'Donnell PH, et al. ASCO 2017 (Abstract No. 4502); 3. Vuky J, et al. ASCO 2018 (Abstract No. 4524).

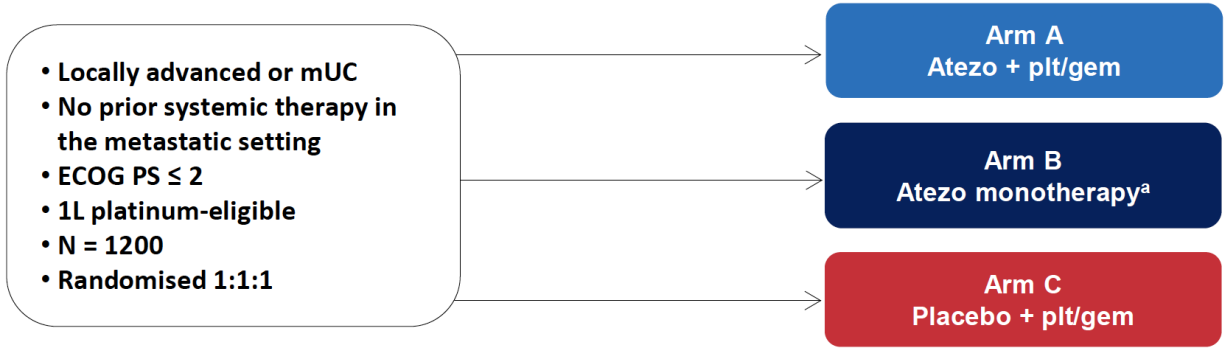
Perspectives

Perspectives



1. NCT02807636. Available at clinicaltrials.gov (accessed October 2019); 2. NCT02516241. Available at clinicaltrials.gov (accessed October 2019); 3. NCT02853305. Available at clinicaltrials.gov (accessed October 2019); 4. NCT03036098. Available at clinicaltrials.gov (accessed October 2019); 5. NCT02603432. Available at clinicaltrials.gov (accessed October 2019).

IMvigor130



Stratification factors:
- PD-L1 IC status (IC0 vs IC1 vs IC2/3)
- Bajorin risk factor score including KPS < 80% vs ≥ 80% and presence of visceral metastases (0 vs 1 vs 2 ± patients with liver metastases)
- Investigator choice of plt/gem (gem + carbo or gem + cis)

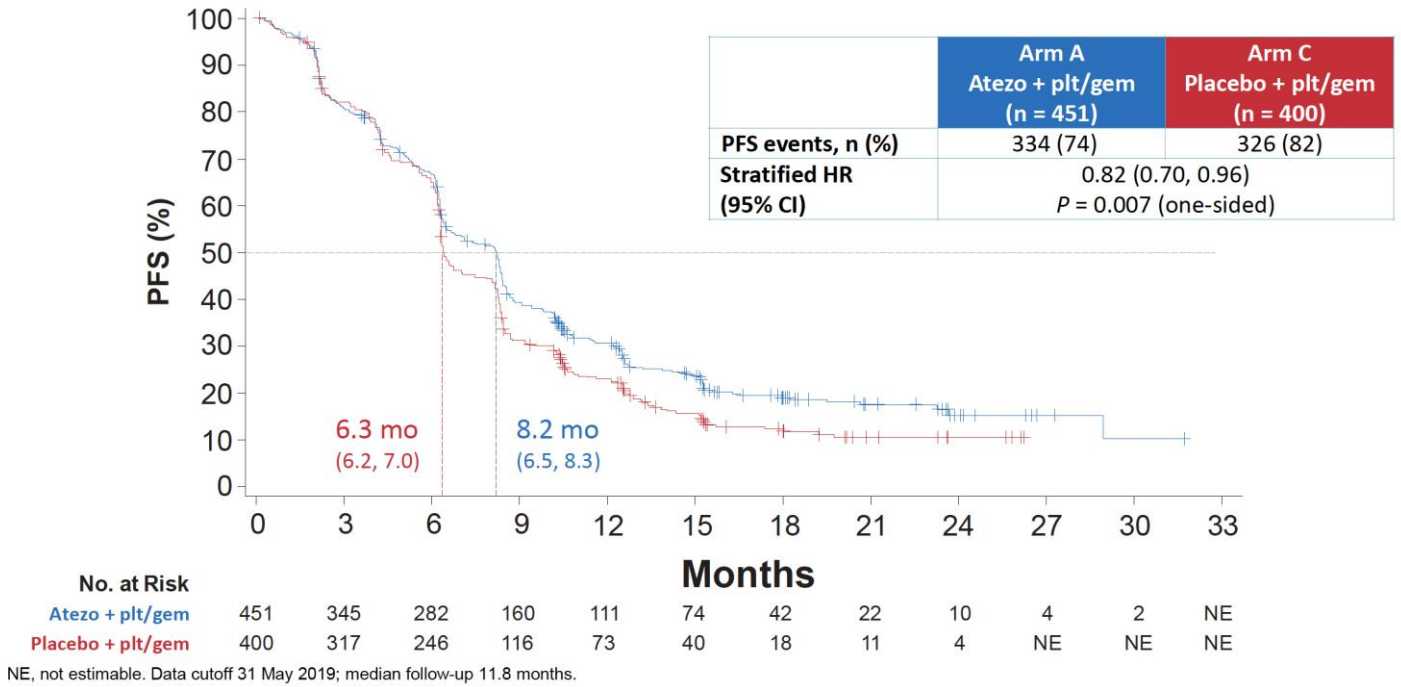
Co-primary endpoints:
- INV-assessed PFS[b] and OS (Arm A vs C)
- OS (Arm B vs C, hierarchical approach)

Key secondary endpoints:
- INV-ORR[b] and DOR
- PFS[b] and OS (Arm B vs C; PD-L1 IC2/3 subgroup)
- Safety

[a] The first 129 patients were randomized 2:1 to Arm A and Arm C per initial study design; Arm B enrolled later. PD-L1 status was unblinded in the final protocol amendment per IMDC recommendation, such that IC0/1 patients received atezo + plt/gem and IC2/3 patients received atezo monotherapy (n = 6).

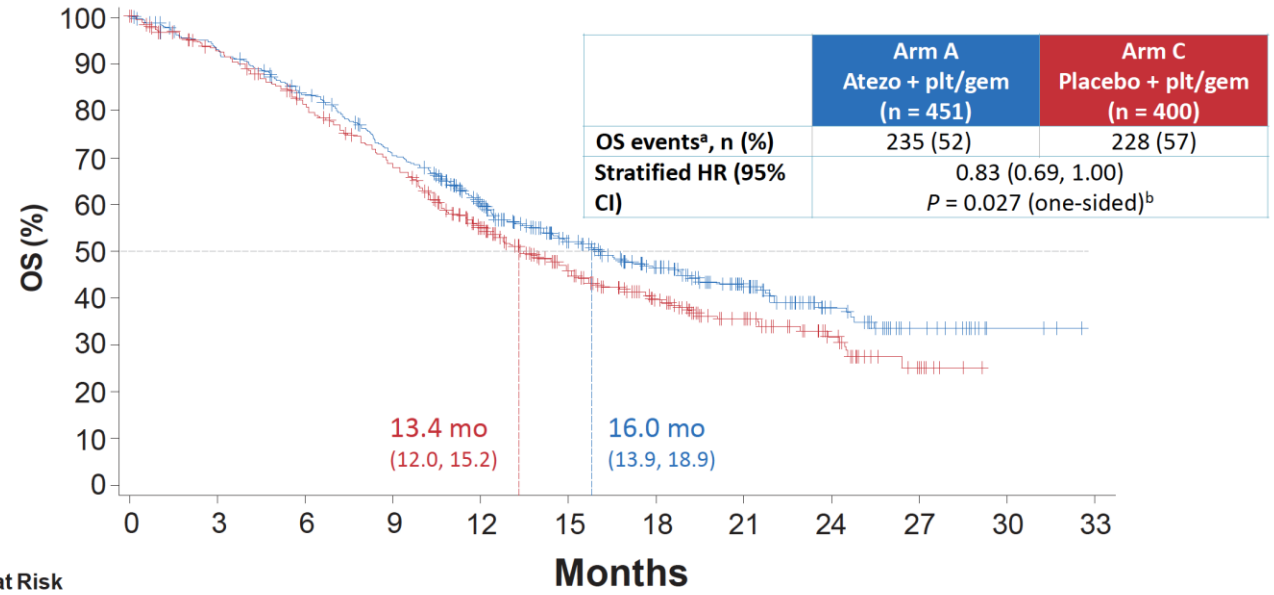
[b] per RECIST 1.1.

IMvigor130 : PFS en ITT CT + IO vs CT



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

IMvigor130 : analyse intermédiaire OS CT + IO vs CT

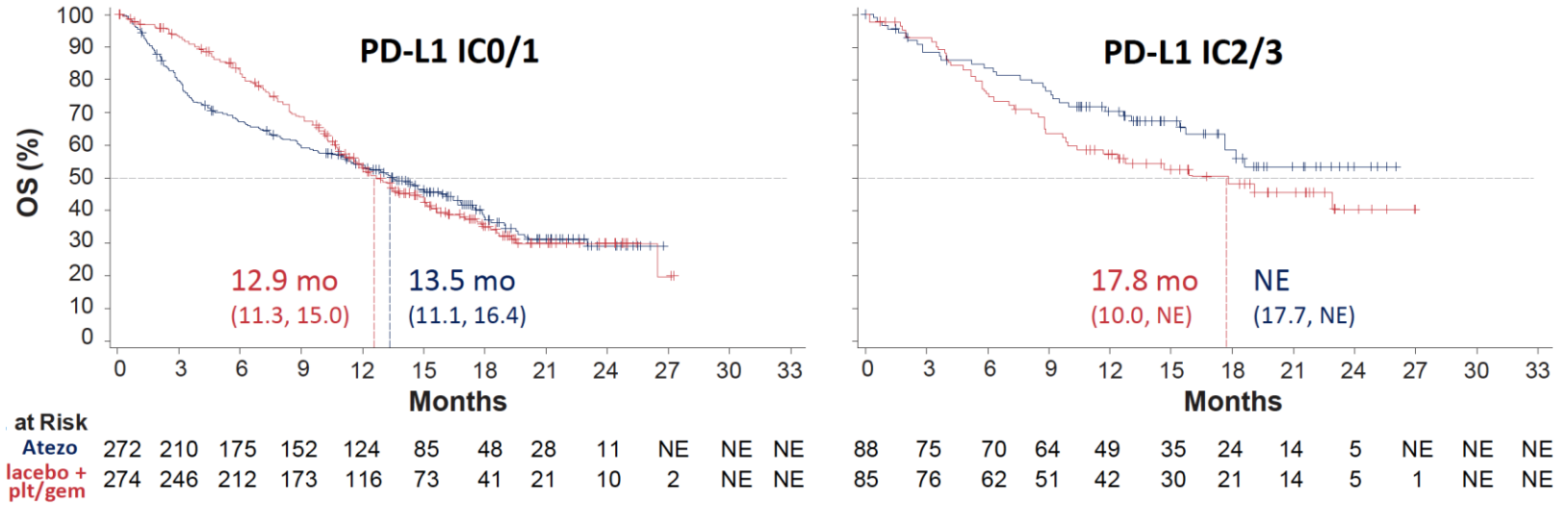


	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b]	

No. at Risk												
Atezo + plt/gem	451	408	360	301	229	163	117	72	36	16	3	NE
Placebo + plt/gem	400	359	308	255	182	123	79	49	25	8	NE	NE

Data cutoff 31 May 2019; median follow-up 11.8 months. [a] 5% of patents from Arm A and 20% of patients from Arm C crossed over to non-protocol immunotherapy.
[b] Did not cross the interim efficacy boundary of 0.007 per the O'Brien-Fleming method.

IMvigor130 : analyse intermédiaire OS CT vs IO en fonction du PD-L1



	Arm B Atezo (n = 272)	Arm C Placebo + plt/gem (n = 274)
OS events, n (%)	158 (58)	156 (57)
Unstratified HR (95% CI)	1.07 (0.86, 1.33)	

	Arm B Atezo (n = 88)	Arm C Placebo + plt/gem (n = 85)
OS events, n (%)	33 (38)	42 (49)
Stratified HR (95% CI)	0.68 (0.43, 1.08)	

Data cutoff 31 May 2019; median follow-up 11.8 months.

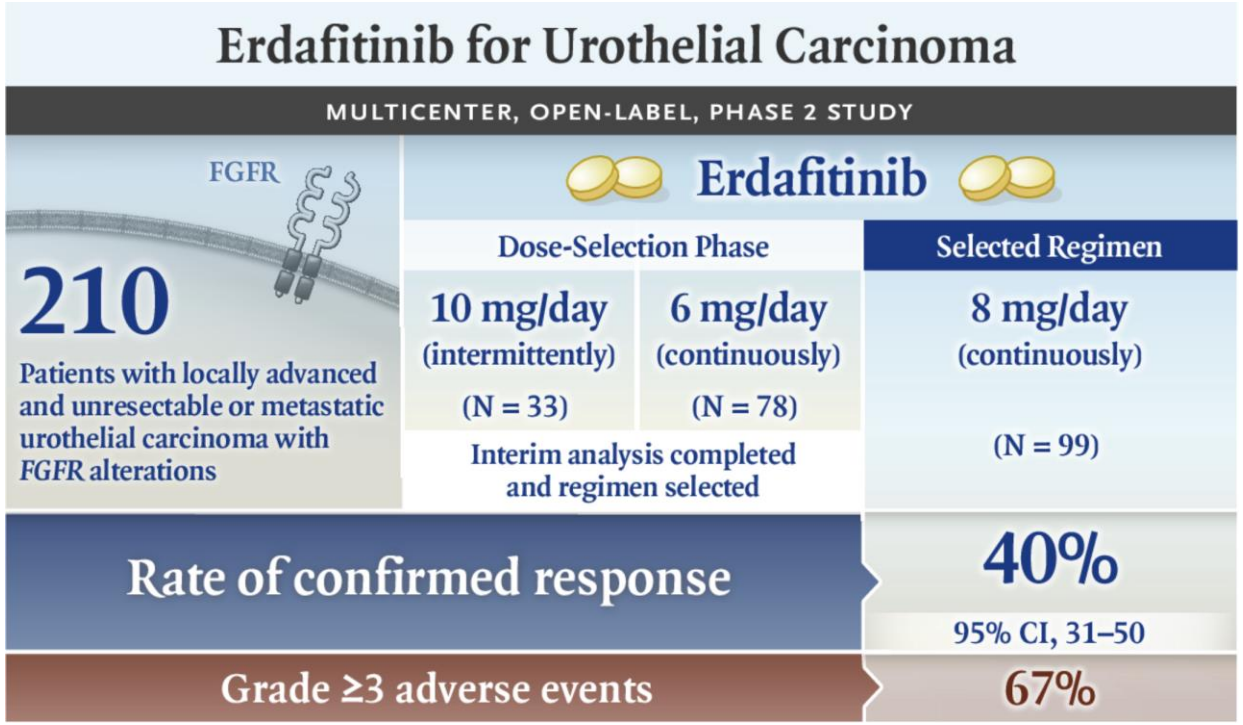
Thérapies ciblées : FGFR

20 % des patients ont une altération de FGFR

PFS 5.5 mois

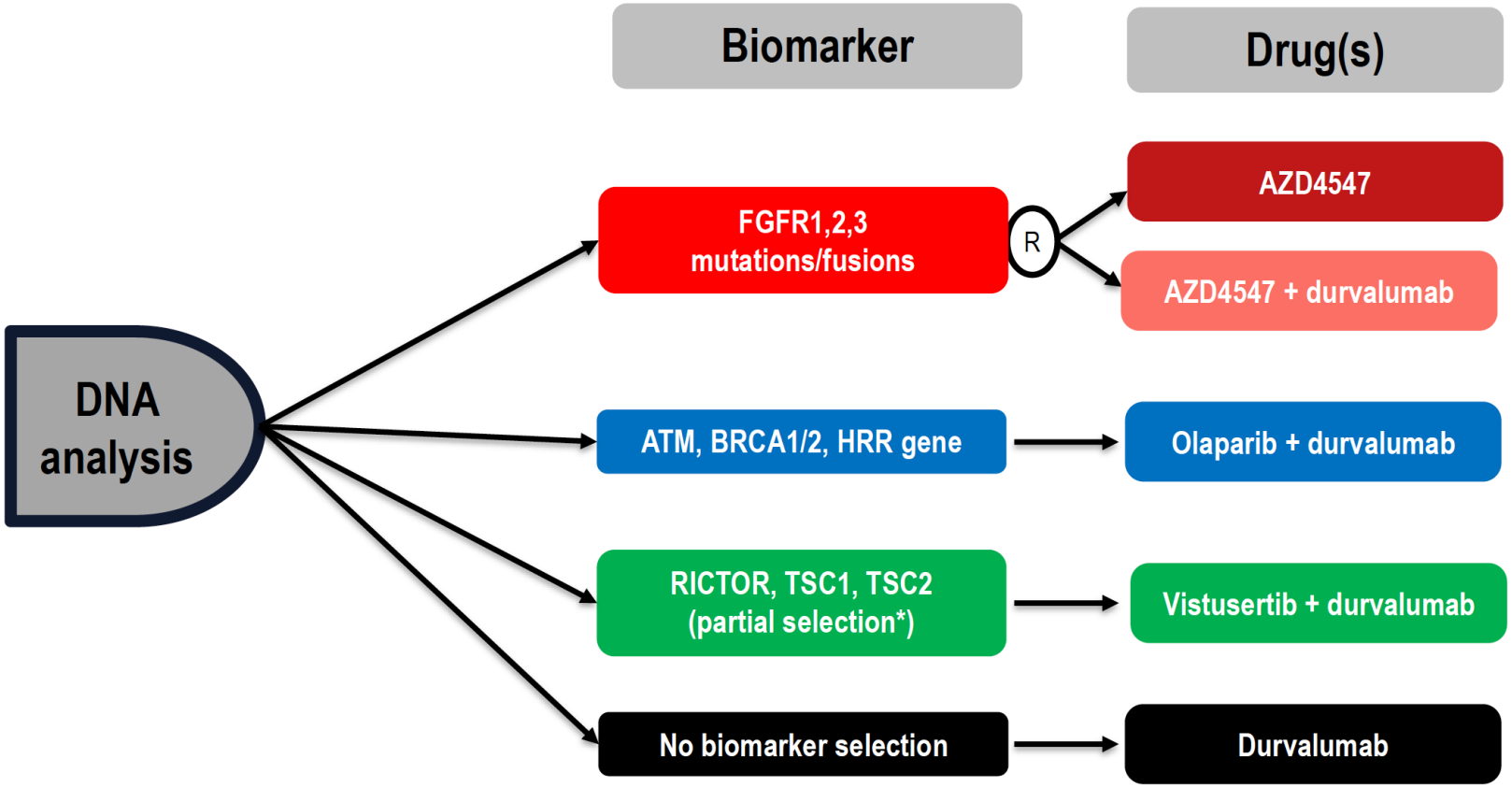
OS 13 mois

Approuvé par la FDA, pas l'EMA



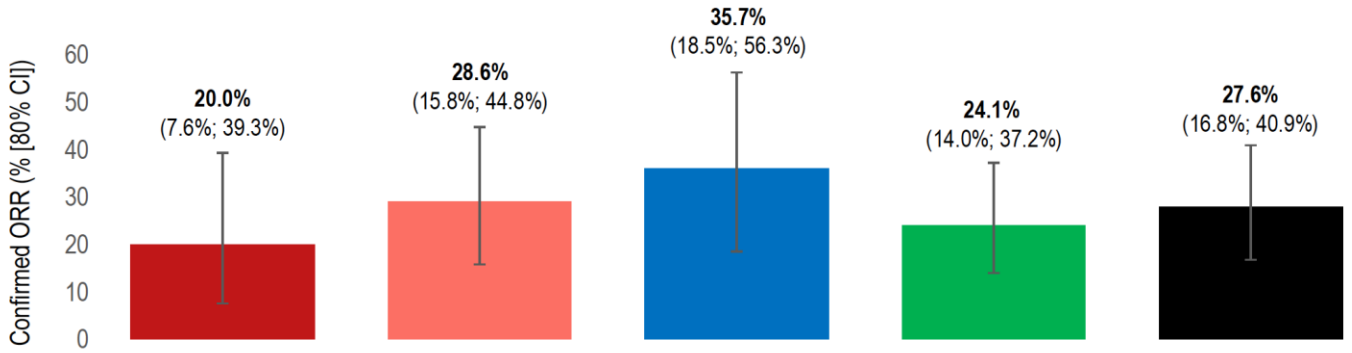
Loriot, NEJM, 2019

BISCAY



Powles, ESMO 2019

BISCAY

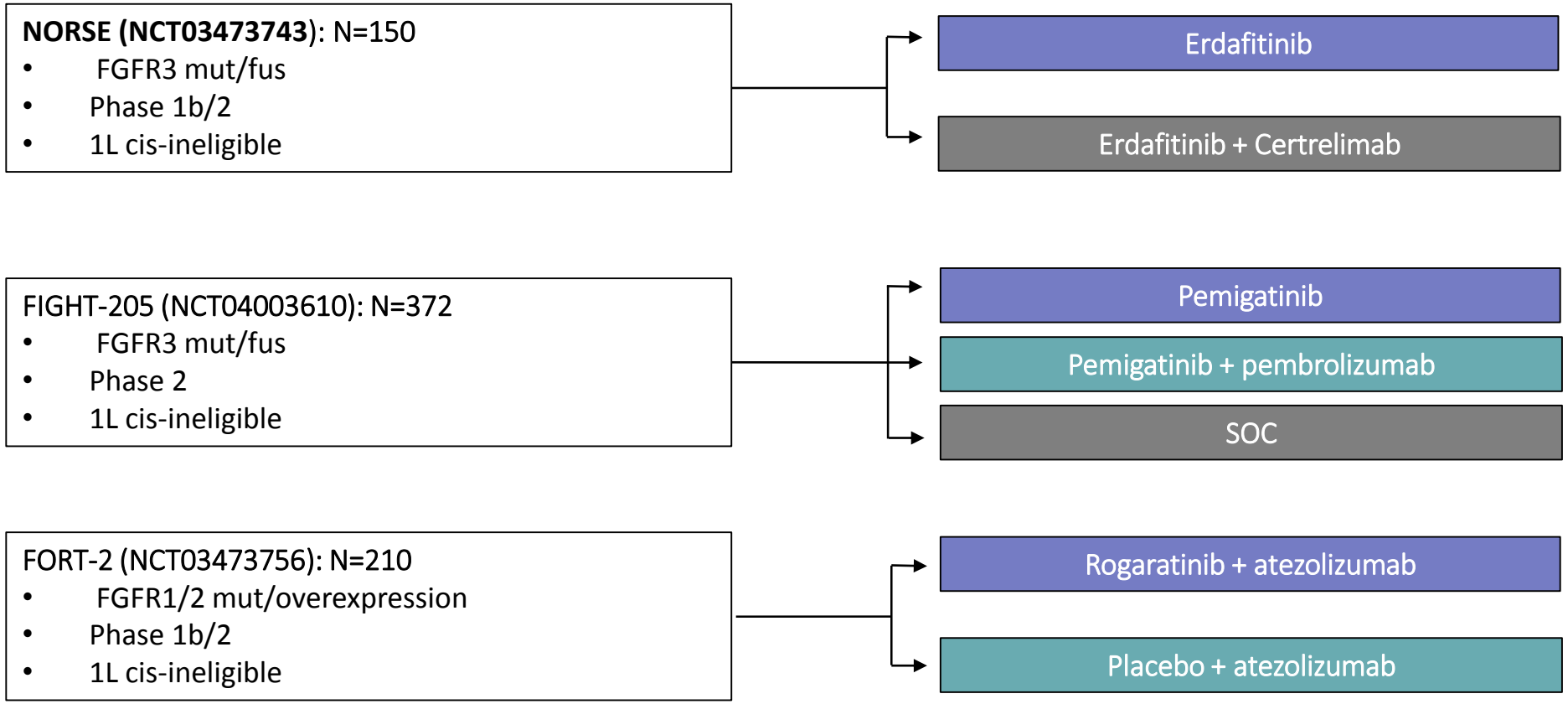


	AZD4547	AZD4547 + durvalumab	Olaparib + durvalumab	Vistusertib + durvalumab	Durvalumab
Number of patients	15	21	14	29	29
Dose of agent	80 mg BID	1500 mg q4w IV 80 mg BID	1500 mg q4w IV 300 mg PO	1500 mg q4w IV 150 mg BID d1,2/w	1500 mg q4w IV
PD-L1 status: +ve	25%	23%	50%	50%	54%
tTMB high >10	23%	5%	54%	43%	18%

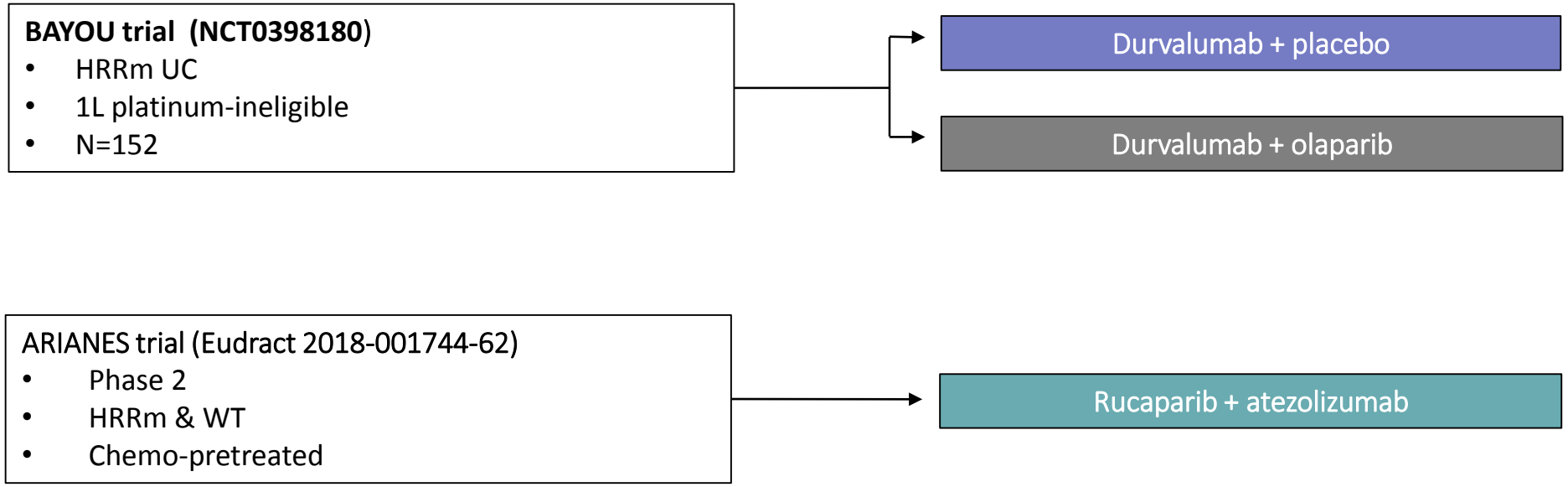
Aucune combinaison n'a atteint les objectifs prédéfinis

Powles, ESMO 2019

Inhibiteurs FGFR + IO



Inhibiteurs PARP + IO



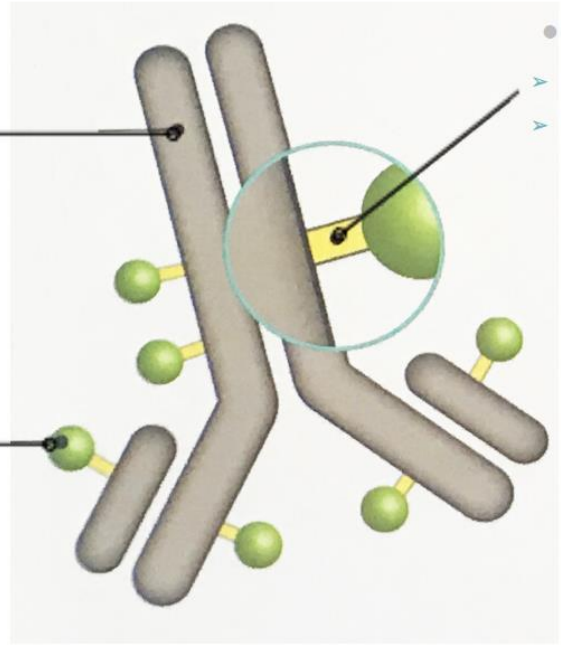
Anticorps conjugués : TROPHY-U-01

Anticorps humanisé anti-Trop 2

- Antigène de surface cellulaire fortement exprimé dans de nombreuses tumeurs dont carcinome urothélial

SN-38 (cytoxique)

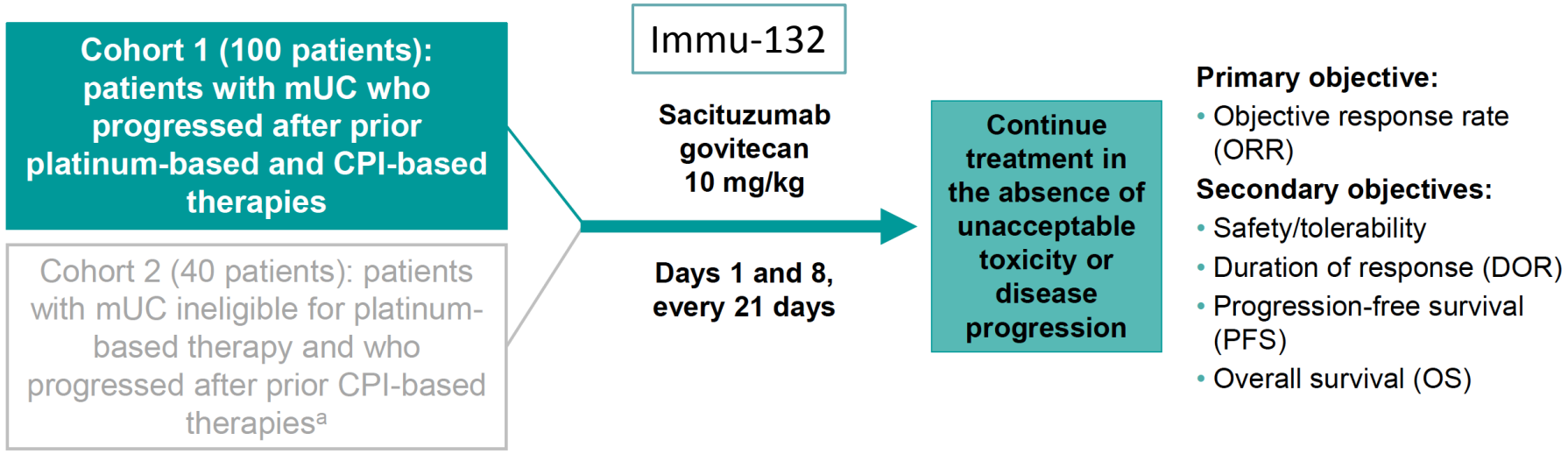
- Metabolite d'un inhibiteur topoisomerase I
- Plus puissant que irinotecan



Linker SN-38

- Lien Hydrolysable
- Ratio médicament/anticorps élevé

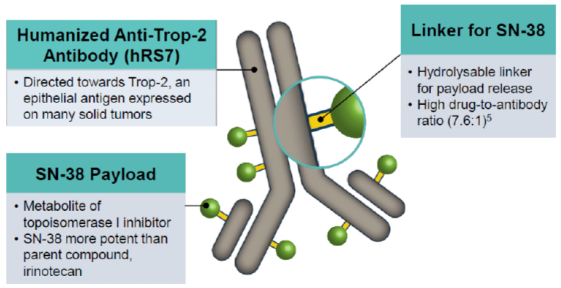
TROPHY-U-01


Cohort 1 (100 patients): patients with mUC who progressed after prior platinum-based and CPI-based therapies
Cohort 2 (40 patients): patients with mUC ineligible for platinum-based therapy and who progressed after prior CPI-based therapies[a]
Immu-132
Sacituzumab govitecan 10 mg/kg
Days 1 and 8, every 21 days
Continue treatment in the absence of unacceptable toxicity or disease progression
Primary objective:
• Objective response rate (ORR)
Secondary objectives:
• Safety/tolerability
• Duration of response (DOR)
• Progression-free survival (PFS)
• Overall survival (OS)

TROPHY-U-01

Sacituzumab Govitecan (SG) Is a Trop-2–Directed Antibody-Drug Conjugate (ADC)

- Trop-2 is an epithelial cell surface antigen highly expressed in UC[1]
- SG is distinct from other ADCs[2-6]:
  - High drug-to-antibody ratio[5]
  - Linker hydrolysis releases SN-38 intracellularly and in the tumor microenvironment[6a]
- SG has shown significant activity across tumor types[3,7-10]
  - Breakthrough therapy designation for mTNBC; accelerated approval submission pending
  - Phase 3 trials ongoing in breast cancer



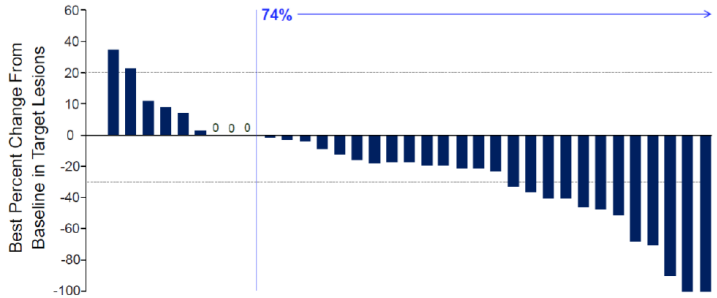
Adverse Events

- Most frequent AEs: diarrhea, nausea, fatigue and neutropenia
  - 24% of pts used G-CSF
- Most frequent grade 3+: neutropenia and anemia
- Most frequent SAEs:
  - Febrile neutropenia and diarrhea in 2 pts each
- 5/45** pts discontinued due to drug-related AEs
  - None due to neutropenia or N/V
  - One patient due to diarrhea
- No treatment-related deaths

Tagawa et al. ESMO 2019

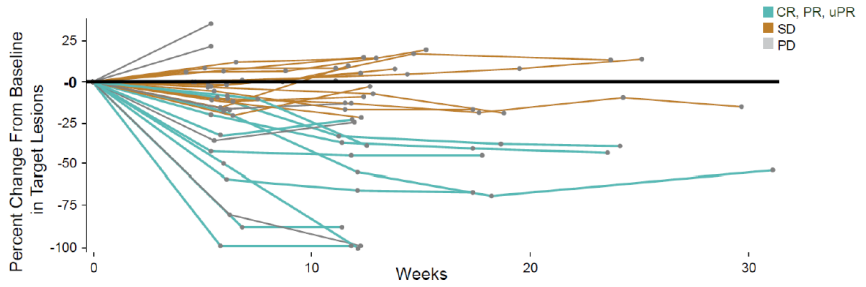
TROPHY-U-01 Cohort 1

74% of Patients Demonstrated a Reduction in Tumor Size



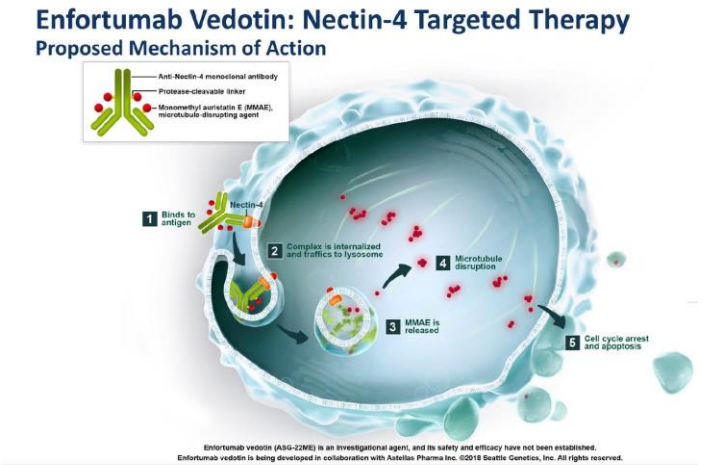
TROPHY-U-01 Cohort 1

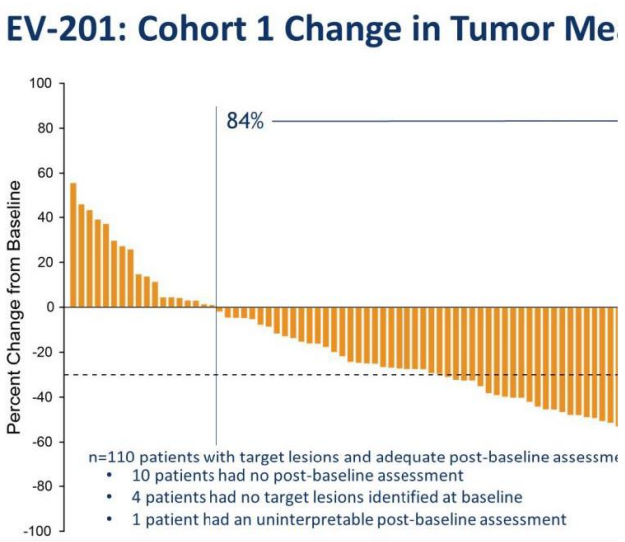
Individual Percent Changes From Baseline in Tumor Size Over Time



- Most pts had reductions in target lesions over time, including many pts with SD or PD

ENFORTUMAB-VEDOTIN





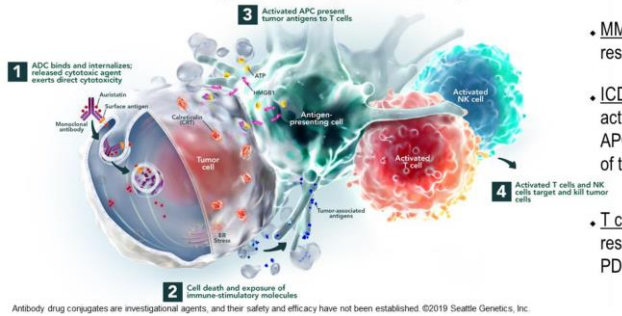
EV-201: Cohort 1 Treatment-Related Adverse Events

Treatment-related AEs by preferred term in ≥20% of patients (any Grade) or ≥5% (≥Grade 3)	Patients (N=125) n (%)	
	Any Grade	≥Grade 3
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	–
Decreased appetite	55 (44)	1 (1)
Dysgeusia	50 (40)	–
Peripheral sensory neuropathy	50 (40)	2 (2)
Nausea	49 (39)	3 (2)
Diarrhea	40 (32)	3 (2)
Dry skin	28 (22)	0
Weight decreased	28 (22)	1 (1)
Rash maculo-papular	27 (22)	5 (4)
Anemia	22 (18)	9 (7)
Neutropenia	13 (10)	10 (8)

- Treatment-related AEs led to few discontinuations (12%)
  - Peripheral sensory neuropathy was the most common (6%)
- 1 treatment-related death reported by the investigator
  - Interstitial lung disease
  - Confounded by high-dose corticosteroid use and suspected *pneumocystis jiroveci* pneumonia

EV-103 : ENFORTUMAB-VEDOTIN + PEMBROLIZUMAB

ADCs[1] linked to monomethyl auristatin E (MMAE) induce immunogenic cell death (ICD) in preclinical and in vitro data, and may enhance anti-tumor immunity



- MMAE disrupts microtubules resulting in ICD due to ER stress
- ICD releases innate immune-activating molecules resulting in APC activation and presentation of tumor antigens to T cells
- T cells mount antigen-specific response augmented by PD-1/L1 inhibitors

Antibody drug conjugates are investigational agents, and their safety and efficacy have not been established. ©2019 Seattle Genetics, Inc.

TREATMENT-RELATED ADVERSE EVENTS OF CLINICAL INTEREST (AECI)

Rates of peripheral neuropathy, rash, and hyperglycemia similar to EV monotherapy in post-platinum, post-PD-1/L1 mUC patients (EV-201, Cohort 1)[1]

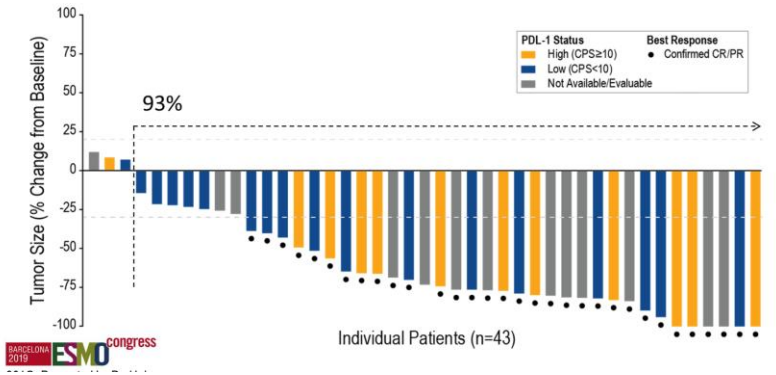
AECI: categorized by related MedDRA terms	Patients (N=45) n (%)		Time to first onset (months) median (min, max)
	Any Grade	≥Grade 3[a]	Any Grade
Peripheral neuropathy	22 (49)	2 (4)	2.2 (1, 6)
Rash	21 (47)	5 (11)	0.4 (0, 7)
Hyperglycemia (non-fasting)	5 (11)	3 (7)	0.5 (0, 3)

[a] No grade 5 events

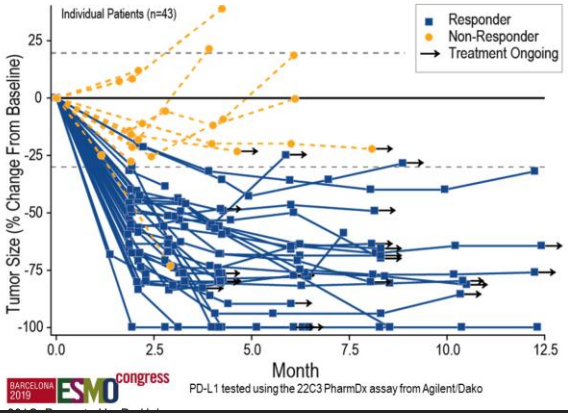
AECI: determined by investigator	Patients (N=45) n (%)	
	Any Grade	≥Grade 3[a]
Immune-mediated AE requiring systemic steroids	9 (20)	5 (11)[b]

[a] No grade 5 events. [b] Events occurred in 1 patient each. Grade 3: pneumonitis, dermatitis bullous, lipase increased, tubulointerstitial nephritis; Grade 4: myasthenia gravis

MAXIMUM PERCENT REDUCTION FROM BASELINE IN SUM OF DIAMETERS OF TARGET LESIONS PER INVESTIGATOR



PERCENT CHANGE FROM BASELINE IN SUM OF DIAMETERS OF TARGET LESIONS PER INVESTIGATOR



PD-L1 tested using the 22C3 PharmDx assay from Agilent/Dako

- 91% of responses observed at first assessment (Week 9±1 week)
- Median time to response: 2.0 months (range: 1.4 to 4.2)
- Duration of response range: 1 to 10.5 months and ongoing
- 22 of 32 responders remain on treatment

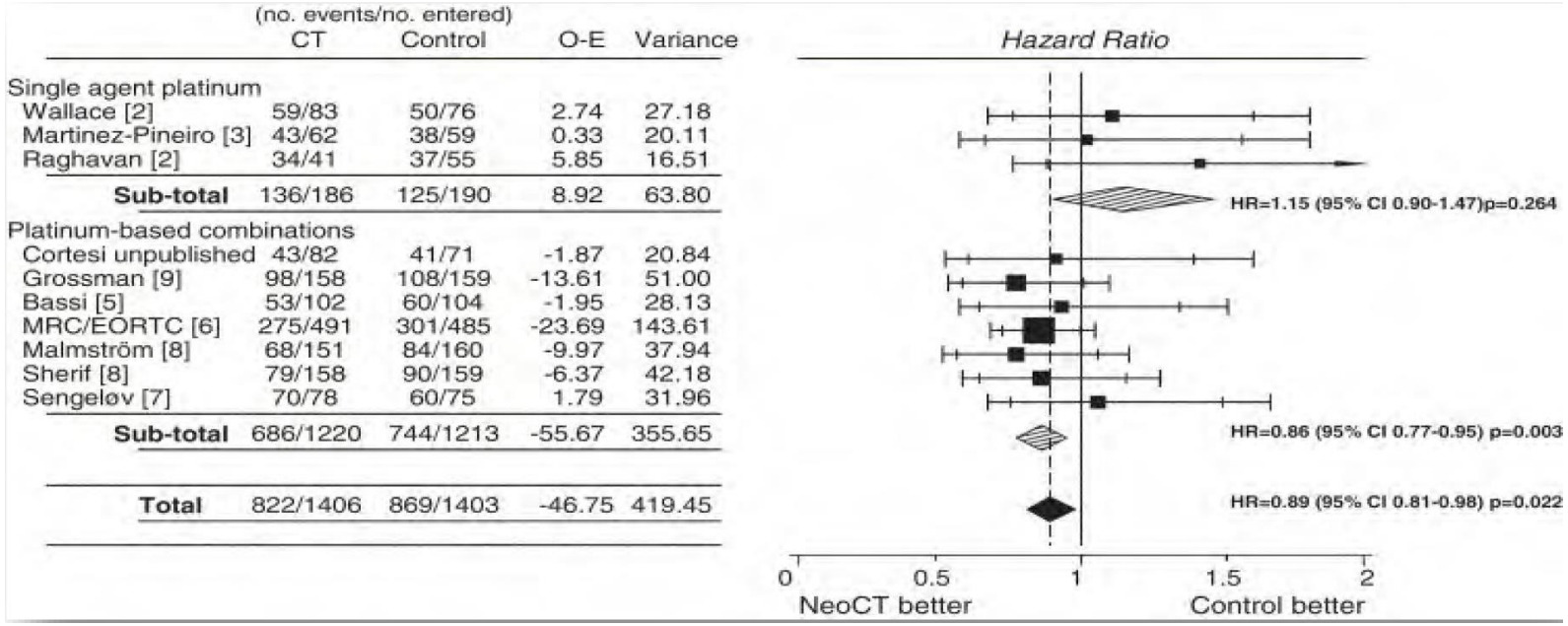
TVIM

Maladie grave : 50 % des patients deviendront métastatique, 66 % de survie à 5 ans

Chirurgie délabrante : la majorité des patients auront une stomie.

Inca 2010

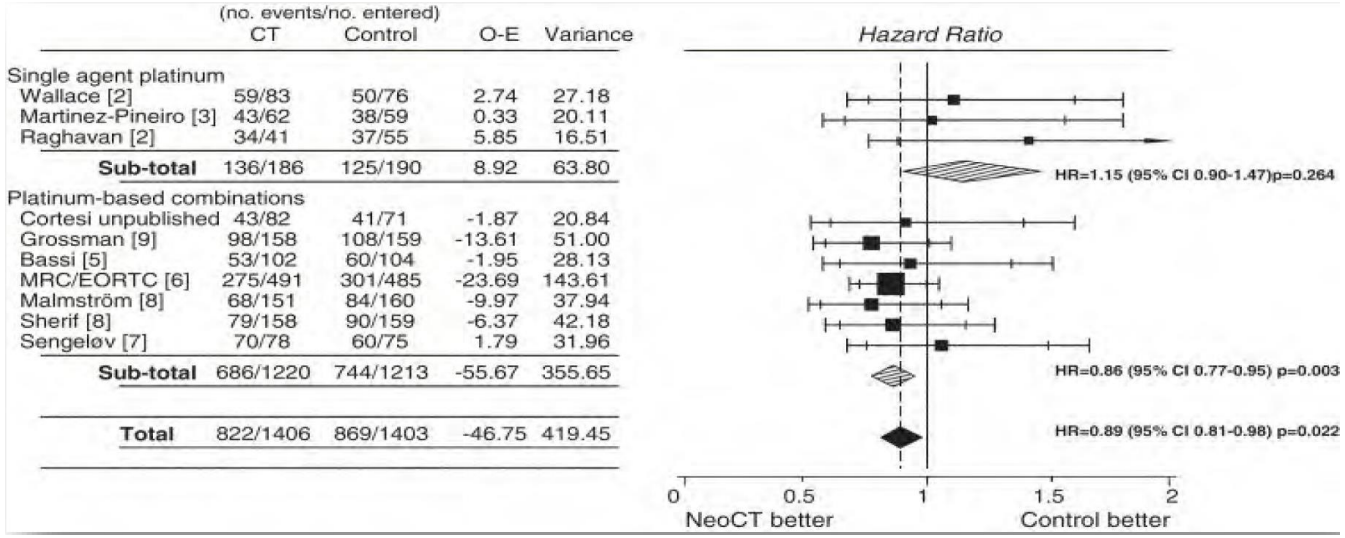
TVIM : stratégies néoadjuvantes



	(no. events/no. entered) CT	Control	O-E	Variance
Single agent platinum				
Wallace [2]	59/83	50/76	2.74	27.18
Martinez-Pineiro [3]	43/62	38/59	0.33	20.11
Raghavan [2]	34/41	37/55	5.85	16.51
Sub-total	136/186	125/190	8.92	63.80
Platinum-based combinations				
Cortesi unpublished	43/82	41/71	-1.87	20.84
Grossman [9]	98/158	108/159	-13.61	51.00
Bassi [5]	53/102	60/104	-1.95	28.13
MRC/EORTC [6]	275/491	301/485	-23.69	143.61
Malmström [8]	68/151	84/160	-9.97	37.94
Sherif [8]	79/158	90/159	-6.37	42.18
Sengeløv [7]	70/78	60/75	1.79	31.96
Sub-total	686/1220	744/1213	-55.67	355.65
Total	822/1406	869/1403	-46.75	419.45

Cochrane systematic review 2005

TVIM : stratégies néoadjuvantes



Bénéfice absolu : 6%
Bénéfice relatif à 10 ans : 16 %

pT0 Rates With CT:

Gem/Cis,
15% to 32%

DD MVAC,
26% to 43%

Mais environ 20-25% de CNA : peu de patients éligibles (< 70 ans, OMS 0-1, cl > 60 ml/min, T2-T4 N0, insuffisance cardiaque < grade III, hypoacousie < grade 2, neuropathie périphérique < grade 2

Cochrane systematic review 2005
Can Urol Assoc J. 2019 Feb; 13(2): 24–28.
Lavery, J Urol 2014;191:898—906
Zargar, Eur Urol 2015;67:241—9,

TVIM : essais néoadjuvants

CPI → Cystectomie

PURE-01 : pembrolizumab
ABACUS : atezolizumab
NABUCO : nivolumab + ipilimumab
PANDORE : pembrolizumab pour les inéligibles au cisplatine

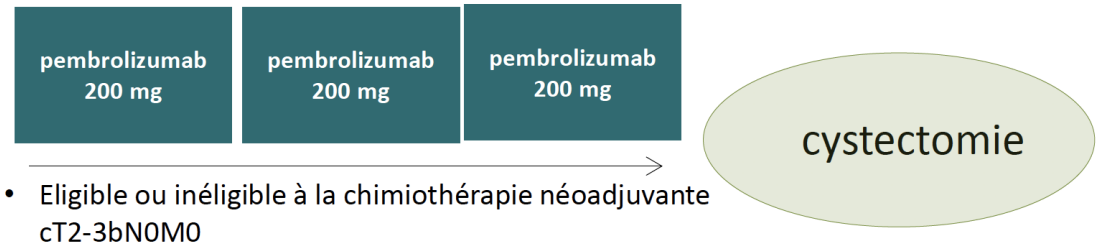
CPI + CNA → Cystectomie

NIAGARA

NEMIO

PURE-01

Stade III
N=50



- Tous les patients ont été opérés (96% dans les 12 semaines)
- 94% ont eu les trois cycles
- 30% de complications opératoires (sepsis, occlusion)
- Grade ¾: 6%

pCR= 42%
pCR = 54% si PDL1+

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

Phase III : KEYNOTE 905 pour les cisplatine non éligibles

Necchi et al. JCO 2019

ABACUS

Stade III
N=95

- inéligible à la chimiothérapie néoadjuvante
- cT2-3bN0M0

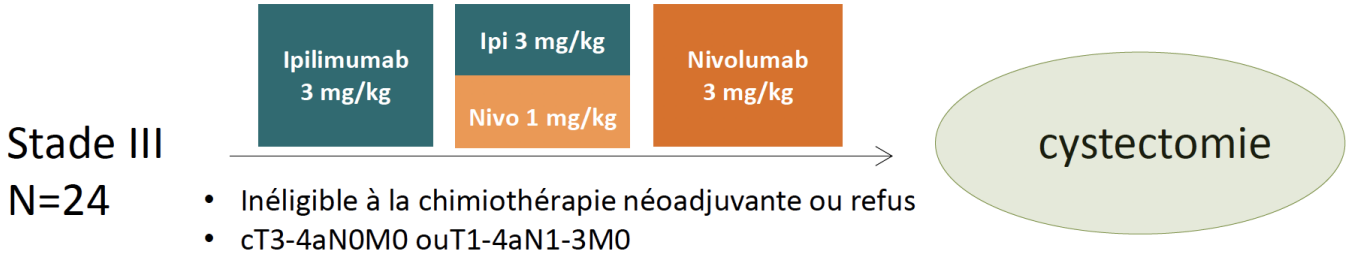
- 8 n'ont pas été opérés
- 2 décès périopératoires
- 17% de complications chirurgicales ¾ (sepsis, occlusion)
- Grade ¾: 11%

pCR= 31%
Survie sans rechute à 1 an: 79%

Signature Th1 associées avec la réponse
Signature fibroblaste – TGFB associées avec la résistance

Powles et al. Nat Med 2019

NABUCO



- Tous les patients ont été opérés (96% dans les 12 semaines)
- 75% ont eu les trois cycles
- Mortalité à 30 jours: 0%
- Mortalité à 90 jours: 4%
- Mais 40% toxicité grade ¾ dont 8% colites

pCR= 46%
pCR = 60% si PDL1+

Van der Heidjen et al. ESMO 2019

TVIM : essais néoadjuvants

CPI → Cystectomie

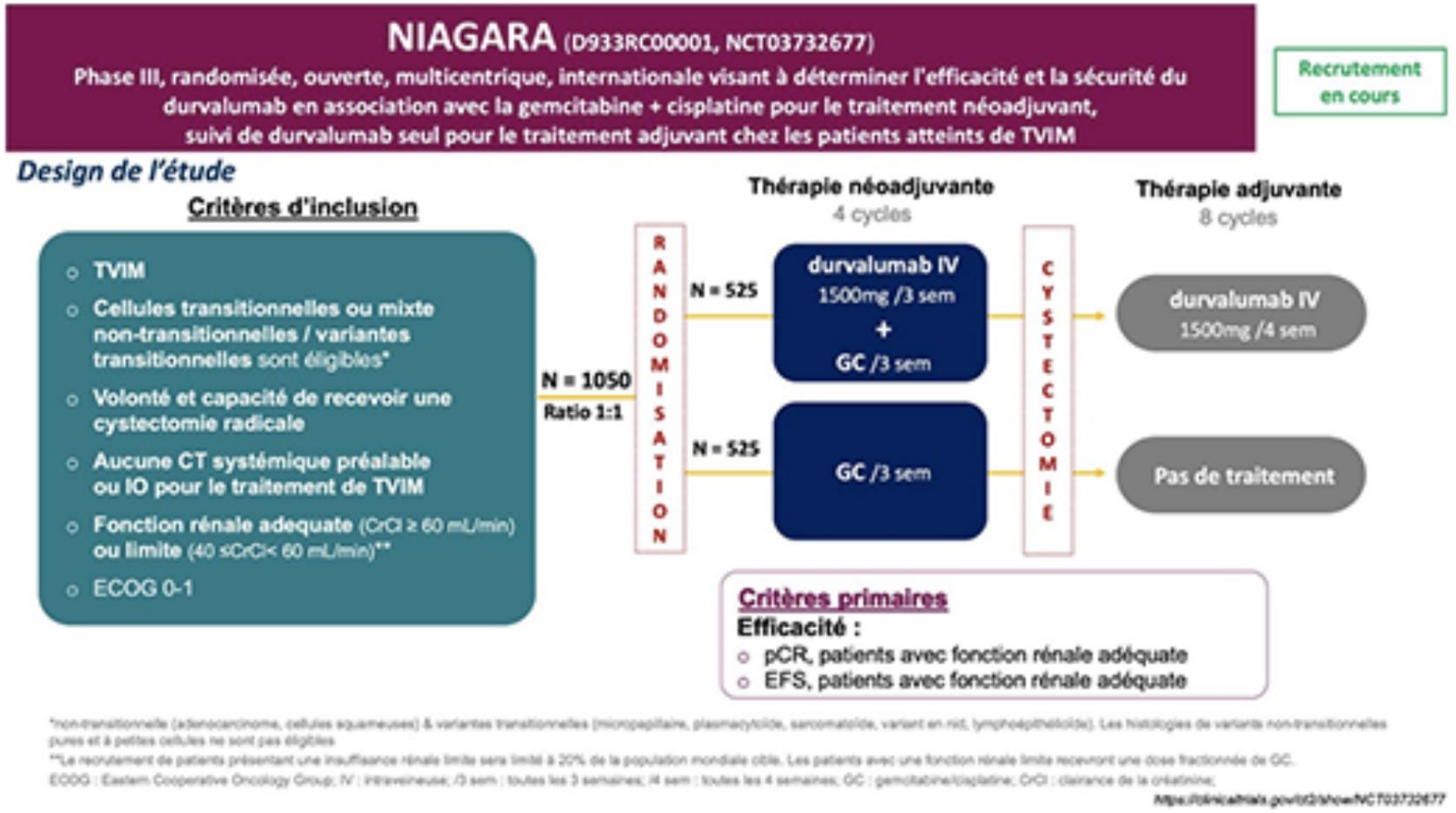
PURE-01 : pembrolizumab
ABACUS : atezolizumab
NABUCO : nivolumab + ipilimumab
PANDORE : pembrolizumab pour les inéligibles au cisplatine

CPI + CNA → Cystectomie

NIAGARA : CG +/- durvalumab

NEMIO : 4 cycles de MVAC dd + durvalumab +/- tremelimumab

NIAGARA



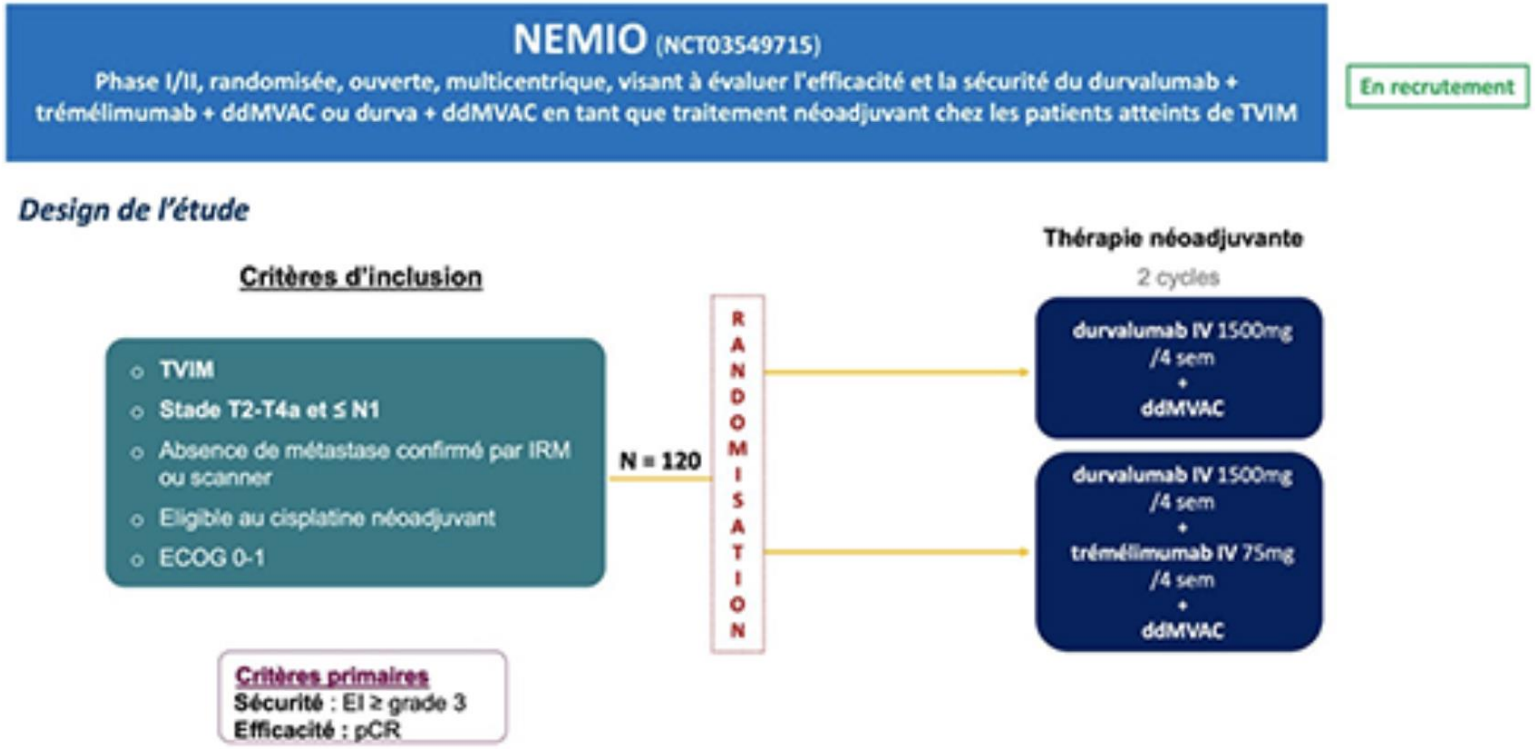
*non-transitionnelle (adenocarcinome, cellules squameuses) & variantes transitionnelles (micropapillaire, plasmacytoïde, sarcomatoïde, variant en nid, lymphoépithélioïde). Les histologies de variants non-transitionnelles pures et à petites cellules ne sont pas éligibles

**Le recrutement de patients présentant une insuffisance rénale limite sera limité à 20% de la population mondiale cible. Les patients avec une fonction rénale limite recevront une dose fractionnée de GC.

ECOG : Eastern Cooperative Oncology Group; IV : intraveineuse; /3 sem : toutes les 3 semaines; /4 sem : toutes les 4 semaines; GC : gemcitabine/cisplatine; CrCl : clairance de la créatinine;

https://clinicaltrials.gov/ct2/show/NCT03732677

NEMIO



TVIM : Tumeur de vessie n'infiltrant pas le muscle; ECOG : Eastern Cooperative Oncology Group; EI : effets indésirables, pcR : taux de réponse complète pathologique; ddMVAC : méthotrexate, vinblastine, doxorubicine, cisplatine; IV : intraveineuse; I4SEM : toutes les 4 semaines; durva : durvalumab

https://clinicaltrials.gov/ct2/show/NCT03549715

TVIM : essais adjuvants

Trial Name	Treatments	Population	Primary Endpoint	ClinicalTrials.gov ID
IMvigor0101	Atezolizumab vs observation	With neoadjuvant: ypT2-4a or ypN+ (ypT2-4 or ypN+ for UTUC) Without neoadjuvant: pT3-T4a or pN+ (pT3-4 or pN+ for UTUC)	DFS	NCT02450331
CheckMate 274	Nivolumab vs placebo	With neoadjuvant: ypT2-pT4a or ypN+ Without neoadjuvant: ypT3-pT4a or ypN+	DFS	NCT02632409
AMBASSADOR	Pembrolizumab vs observation	With neoadjuvant: ≥ pT2 and/or N+ Without neoadjuvant: ≥ pT3 or pN+	DFS, OS	NCT03244384

TVIM : préservation d'organe

Aucun essai de comparaison directe avec chimiothérapie néoadjuvante + cystectomie

Rationnel avec d'autres localisations : ORL, canal anal…

Population sélectionnée : asymptomatique, résection maximale, unifocal, pas de CIS, pas DPC…

Ne pas sous-utiliser la radio-chimiothérapie concomitante

ASCO GU 2019 : Dr Efstathiou

TVNIM

Standard haut risque : BCG thérapie jusqu'à 3 ans

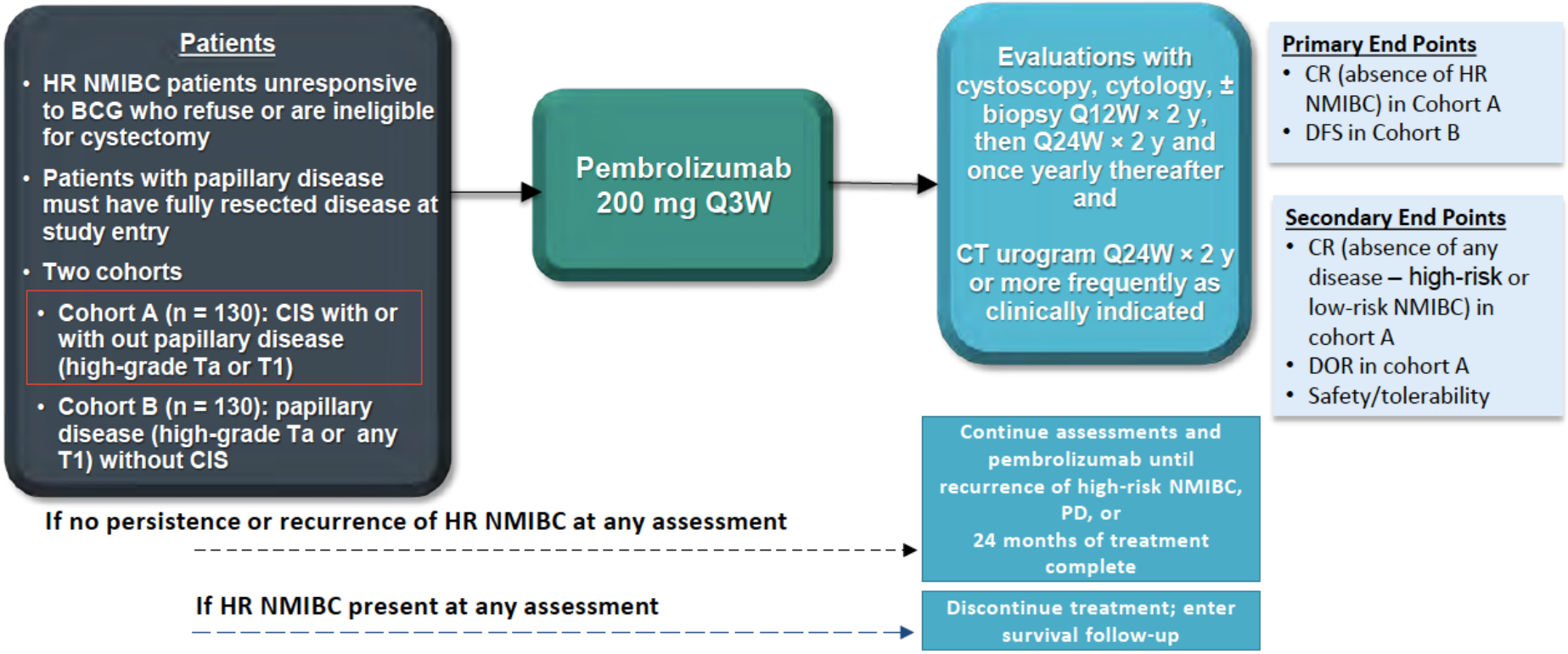
Mais :

40 % de récidive invasive

20 à 30 % de récidive métastatique

➔ Intérêt de l'immunothérapie « moderne » ?

KEYNOTE 057


Patients
HR NMIBC patients unresponsive to BCG who refuse or are ineligible for cystectomy
Patients with papillary disease must have fully resected disease at study entry
Two cohorts
Cohort A (n = 130): CIS with or with out papillary disease (high-grade Ta or T1)
Cohort B (n = 130): papillary disease (high-grade Ta or any T1) without CIS
Pembrolizumab 200 mg Q3W
Evaluations with cystoscopy, cytology, ± biopsy Q12W × 2 y, then Q24W × 2 y and once yearly thereafter and
CT urogram Q24W × 2 y or more frequently as clinically indicated
Primary End Points
CR (absence of HR NMIBC) in Cohort A
DFS in Cohort B
Secondary End Points
CR (absence of any disease – high-risk or low-risk NMIBC) in cohort A
DOR in cohort A
Safety/tolerability
If no persistence or recurrence of HR NMIBC at any assessment
Continue assessments and pembrolizumab until recurrence of high-risk NMIBC, PD, or 24 months of treatment complete
If HR NMIBC present at any assessment
Discontinue treatment; enter survival follow-up

KEYNOTE 057

Médiane de suivi : 16.7 mois

Overall Response Rate at Month 3[a]

Response	Total Population (N = 102)		
	n	%	95% CI
CR	**41**	**40.2**	**30.6-50.4**
Non-CR	57	55.9	45.7-65.7
Persistent[b]	41	40.2	30.6-50.4
Recurrent[c]	6	5.9	2.2-12.4
NMIBC stage progression[d]	9	8.8	4.1-16.1
Non-bladder malignancy[e]	1	1.0	0.0-5.3
Progression to T2	0	0	NA-NA
Nonevaluable[f]	4	3.9	1.1-9.7

KEYNOTE 057

Aucune évolution métastatique
12.7% d'effets indésirables grade 3-4
7.8% d'arrêt pour toxicité

➔ Essai de phase III KEYNOTE-676 : BCG vs BCG + pembrolizumab dans les TVNIM à haut risque

KEYNOTE 057

Aucune évolution métastatique
12.7% d'effets indésirables grade 3-4
7.8% d'arrêt pour toxicité

➔ Essai de phase III KEYNOTE-676 : BCG vs BCG + pembrolizumab dans les TVNIM à haut risque

Arrivée des CPI dans les TVNIM = implication des oncologues dans les TVNIM

Autres phases I/II : BCG + atezolizumab, durvalumab seul vs durvalumab + BCG vs durvalumab + RTE…

Take home messages

Nouveautés : PEMBROLIZUMAB 2ème ligne après platine

Perspectives immunothérapies :
- Pour les TVNIM
- En néo adjuvant
- En adjuvant
- En 1ère ligne pour les PDL1+, 2ème ligne , cis-éligible, non éligible, doublet d'immuno, combo chimio-immuno, en switch maintenance…

Thérapies cibles (FGFR, inhibiteur de PARP) : avenir en monothérapie ? Plutôt combo ?

Ac-conjugués : prometteurs, attente de phase II/III

Take home messages

Nouveautés : PEMBROLIZUMAB 2ème ligne après platine

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- En adjuvant
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ON PROGRESSE !

Thérapies cibles (FGFR, inhibiteur de PARP) : avenir en monothérapie ? Plutôt combo ?

Ac-conjugués : prometteurs, attente de phase II/III