Cancers digestifs hors colorectal : une immunothérapie pour tous?

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Institut PAOLI-CALMETTES
17/11/2023 - JS de Saint Brieuc

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avancés

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Liens d'intérêt- C. de la Fouchardière

Amgen,
Astellas,
Astra-Zeneca
Bayer,
Beigene
Bristol-Myers Squibb,
Daichi-Sankyo
Eisai,
Incyte,
Ipsen,
Lilly,
Merck,
MSD,
Pierre Fabre Oncologie,
Roche,
Servier
Takeda

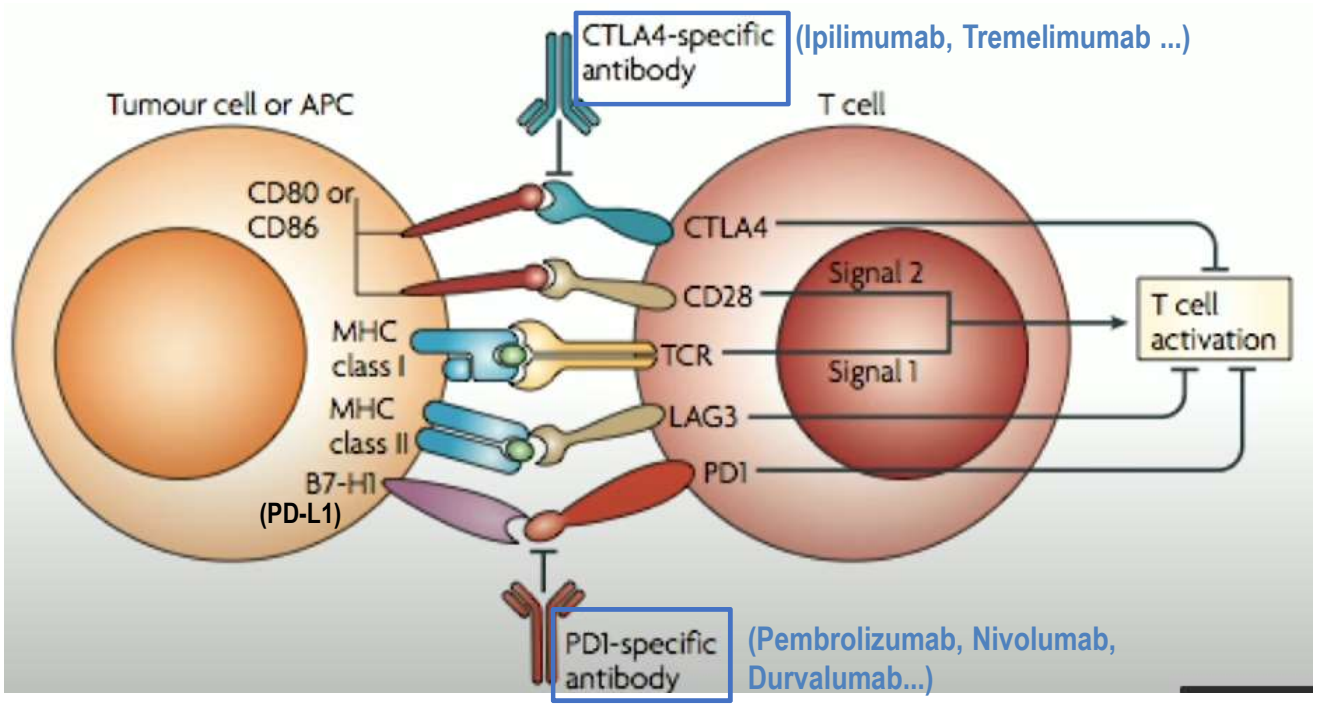
Plan

Introduction

1. Cancers œsogastriques
2. Cancers hépato-biliaires
   - Cholangiocarcinomes
   - Carcinomes hépato-cellulaires
3. Tumeurs MSI (hors colorectal)

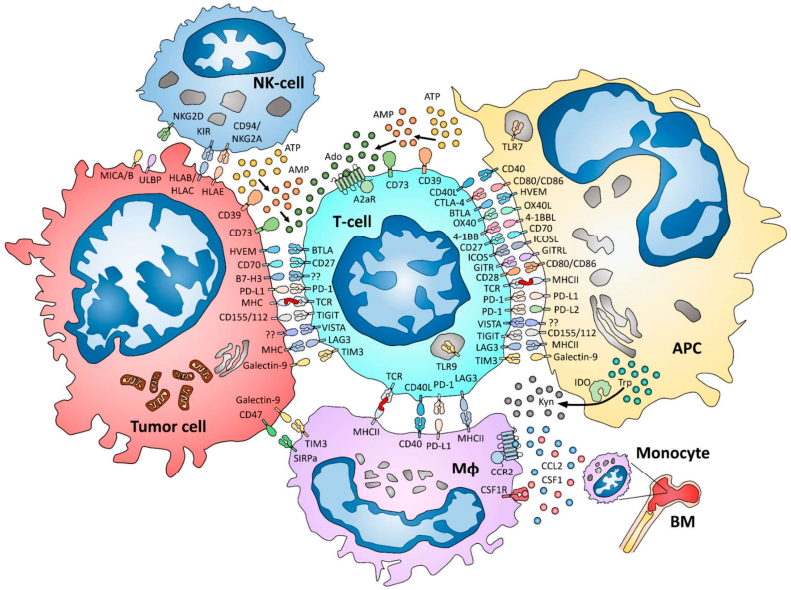
Conclusion

Immunothérapie

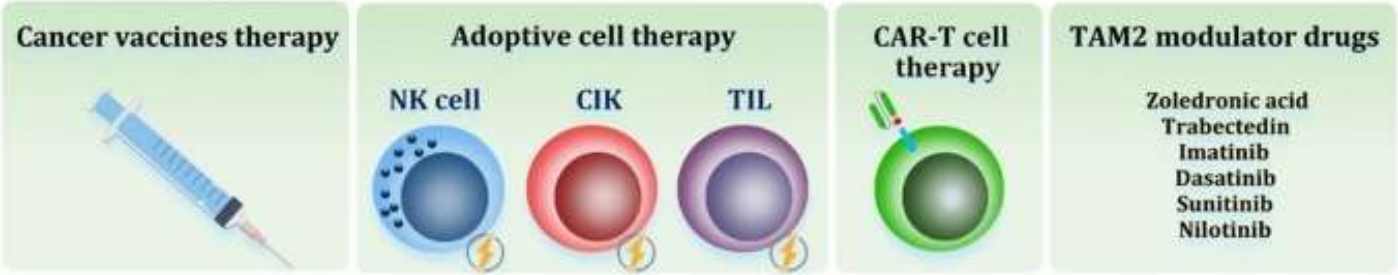


Other checkpoint inhibitors/modulators in development

- LAG3
- TIGIT
- CD28
- TIM3
- ICOS
- OX40
- VISTA ....



Other IO agents in development



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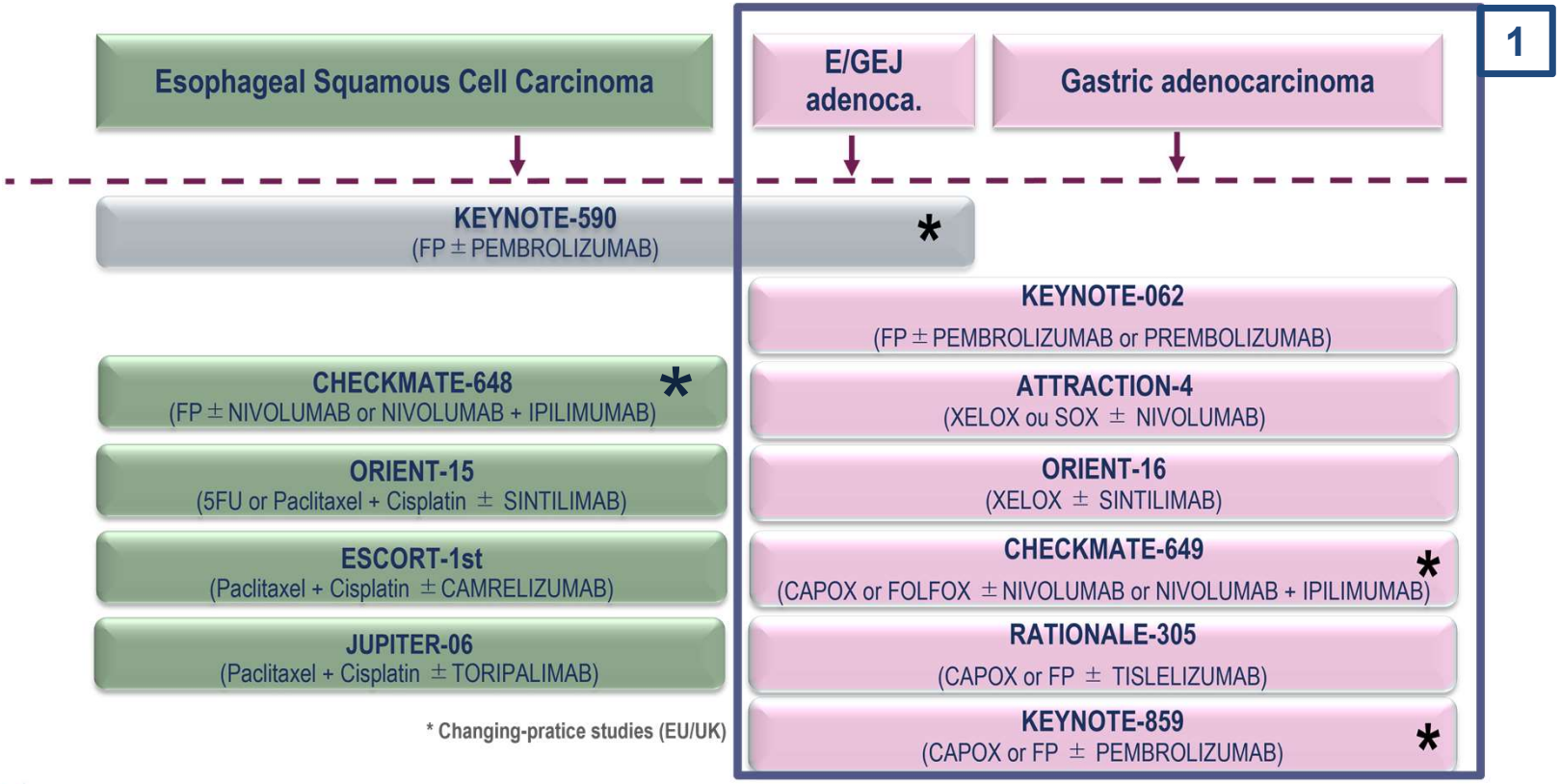
1- Cancers œsogastriques

Immunothérapie dans les cancers œsogastriques avancés

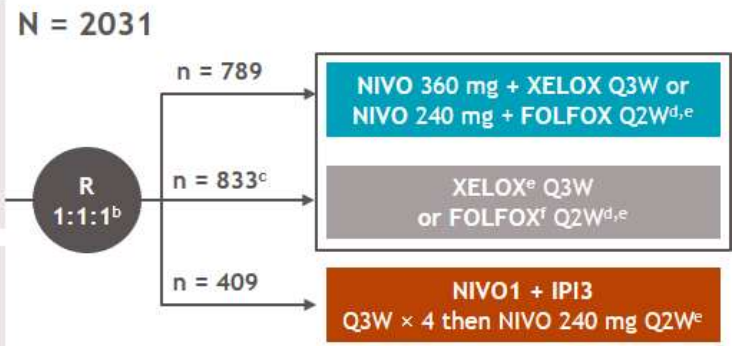


CHECKMATE-649

Etude de phase III randomisée, 1ère ligne
Estomac-Jonction-Œsophage **HER2 nég.**

Key eligibility criteria:
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/esophageal adenocarcinoma
- No known *HER2*-positive status
- ECOG PS 0-1

Stratification factors:
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[a])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



- **Objectif principal = OS and PFS (CPS≥5)**
- **Expression PD-L1 : test Dako PD-L1 28-8 pharmDx**

Caractéristiques patients	NIVO + CT (n=789)	CT (n=792)
Age médian (ans)	63 (18-99)	62 (23-90)
Homme (%)	70	72
Non Asiatique (%)	75	76
Tumeur Ive (%)		
Gastrique	70	69
JOG	30	31
FOLFOX/XELOX (%)	51/41	52/48
CPS-PD-L1 ≥ 5 (%)	60	61
MSI (%)	4	3

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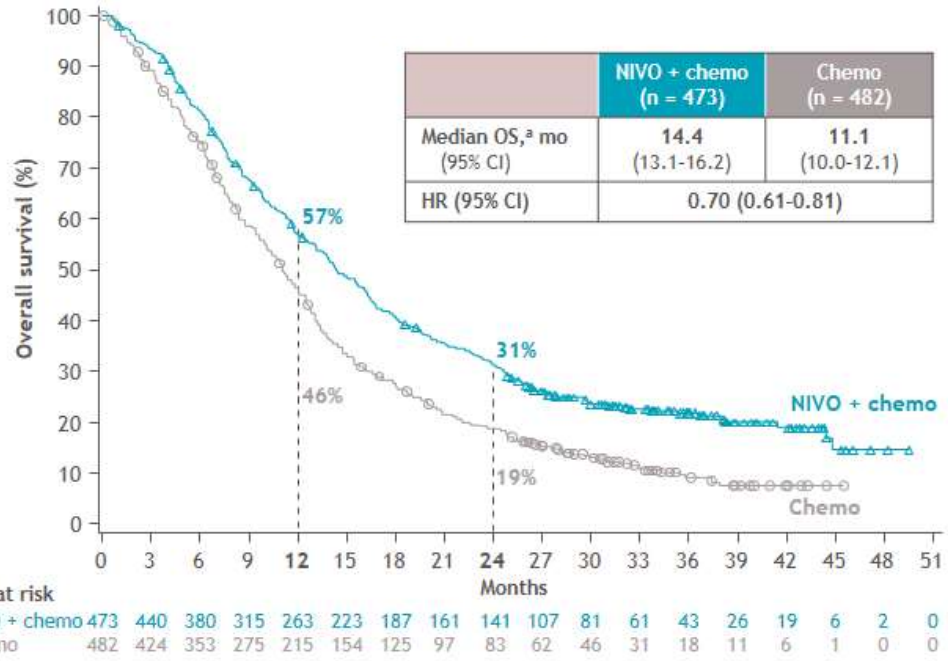
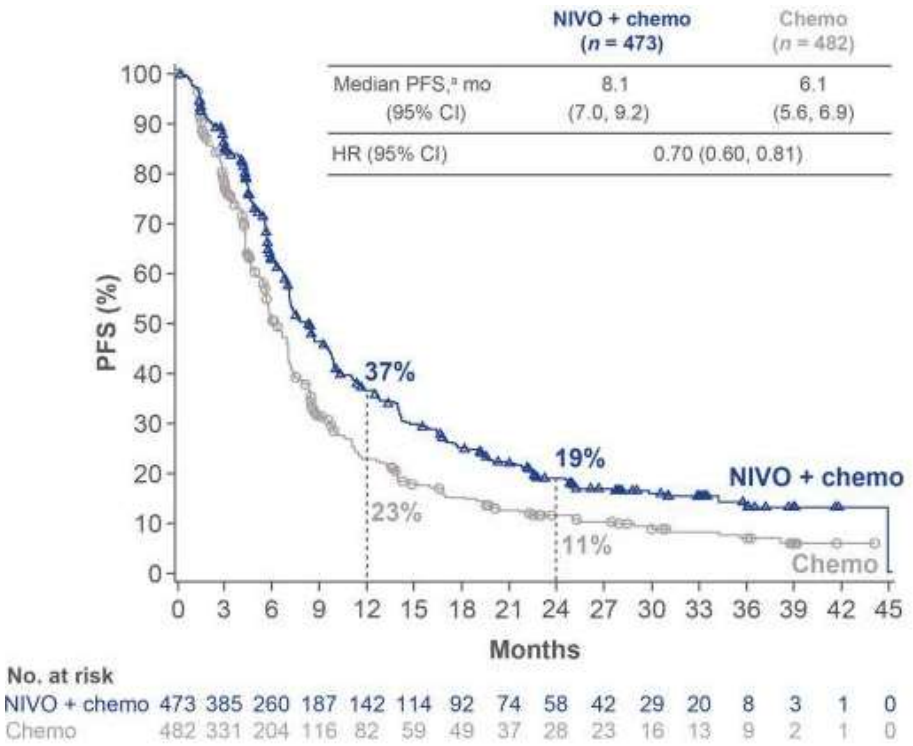
Janjigian YY et al. The Lancet 2021, Shitara K et al, Nature 2022

CHECKMATE-649

Co-critère principal de jugement (OS et PFS) – CPS-PD-L1 ≥5



	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS,[a] mo (95% CI)	14.4 (13.1-16.2)	11.1 (10.0-12.1)
HR (95% CI)	0.70 (0.61-0.81)	



	NIVO + chemo (n = 473)	Chemo (n = 482)
Median PFS,[a] mo (95% CI)	8.1 (7.0, 9.2)	6.1 (5.6, 6.9)
HR (95% CI)	0.70 (0.60, 0.81)	

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CHECKMATE-649

Taux de réponse et durée de réponse

Variable	PD-L1 CPS ≥5 Nivolumab plus chemotherapy (*n* = 378)[a]	Chemotherapy (*n* = 390)[a]
Objective response rate, *n* (%)	226 (60)	176 (45)
95% CI	55, 65	40, 50
Best overall response, *n* (%)[b]		
Complete response	49 (13)	26 (7)
Partial response	177 (47)	150 (38)
Stable disease	105 (28)	132 (34)
Progressive disease	26 (7)	42 (11)
Not evaluable	21 (6)	40 (10)
Median time to response (range), months[c]	1.5 (0.8–10.2)	1.4 (1.0–13.7)

Durée médiane de réponse (mois)	Nivo + CT	CT
CPS-PDL1 ≥ 5%	**9.7** [8.2-12.4]	**7.0** [5.6-7.9]
Tous patients	8.5 [7.7-10.2]	6.9 [5.8-7.2]

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Effets indésirables

Tous pts traités n (%)	NIVO + chimio (n=782)		Chimio (n =767)	
	Tous grades	Grade 3/4	Tous grades	Grade 3/4
Toutes toxicités	739 (95)	473 (60)	682 (89)	346 (45)
Toxicités sévères	176 (23)	134 (17)	95 (12)	78 (10)
Toxicités amenant à une interruption de traitement	331 (42)	147 (19)	198 (26)	73 (10)
Décès reliés au traitement	16 (2)		4 (< 1)	

- Pas de nouveau signal de toxicité
- Principales toxicités Grade 3/4
  - **NIVO + CT :** neutropénie (16%), baisse des PNN (11%), anémie (6%), augmentation de la lipase (6%)
  - **Chimio :** neutropénie (13%), baisse des PNN (9%), diarrhée (3%), neuropathie périphérique (3%), anémie (3%), vomissements (3%)

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Janjigian YY et al. The Lancet 2021, Shitara K et al, Nature 2022
YY Janjigian et al, ASCO GI® 2023, Abs #291

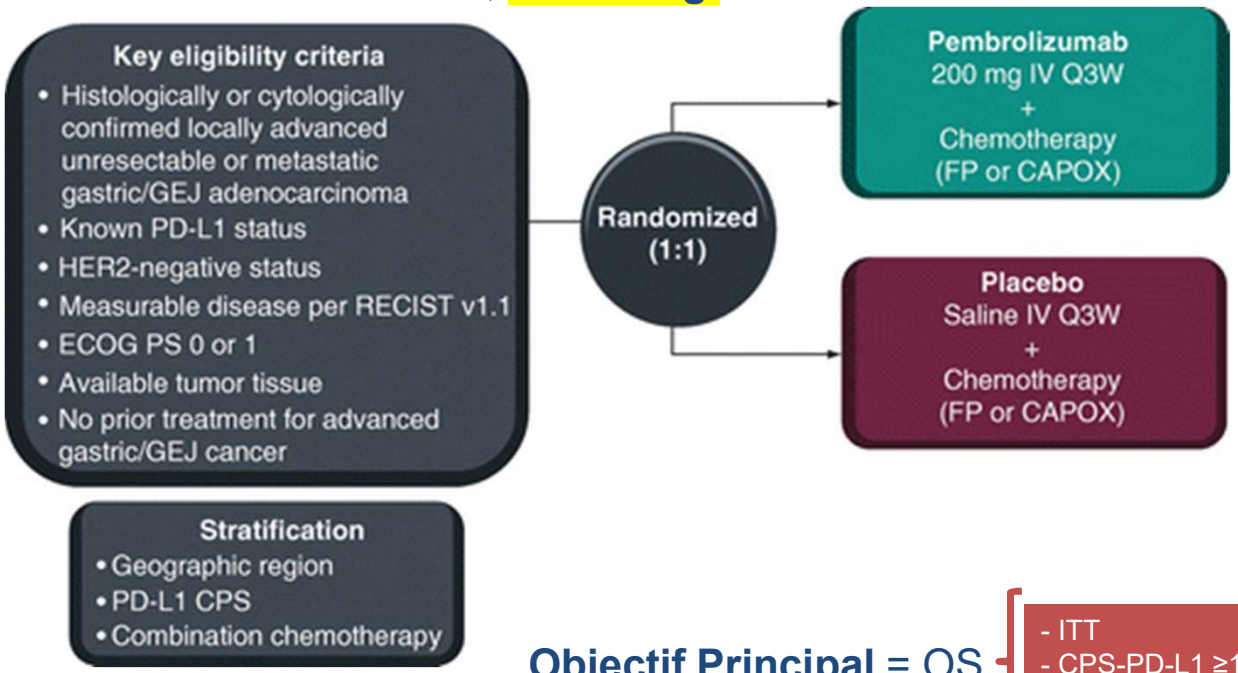
CHECKMATE-649

- Accord **FDA** 16/04/2021
- Accord **EMA** 19/10/2021
- **17/02/2022** : accès précoce en France
- **07/06/2022** : avis positif CEESP

« **Nivolumab indiqué** en association à une chimiothérapie combinée à base de **fluoropyrimidine et de sels de platine**, en **1ère ligne** de traitement, dans le traitement des patients adultes atteints d'un **adénocarcinome gastrique**, de la **jonction œsogastrique** ou de l'**œsophage** avancé ou métastatique, HER-2 négatif, dont les tumeurs expriment **PD-L1 avec un CPS≥5** ».

KEYNOTE-859

Etude de phase III randomisée, 1ère ligne
Estomac-Jonction, **HER2 nég.**



Objectif Principal = OS
- ITT
- CPS-PD-L1 ≥1
- CPS-PD-L1 ≥10

Objectifs secondaires = PFS ORR, DOR et tolérance

Caractéristiques patients	Pembro + CT (n=790)	Placebo + CT (n=789)
Age médian (ans)	61 (52-67)	62 (52-69)
Homme (%)	67	69
Non Asiatique (%)	66	66
Tumeur Ive (%)		
Gastrique	81	76
JOG	19	23
FP/CAPOX (%)	14/86	14/86
CPS-PDL1 ≥ 10	35	34
MSI (%)	5	4

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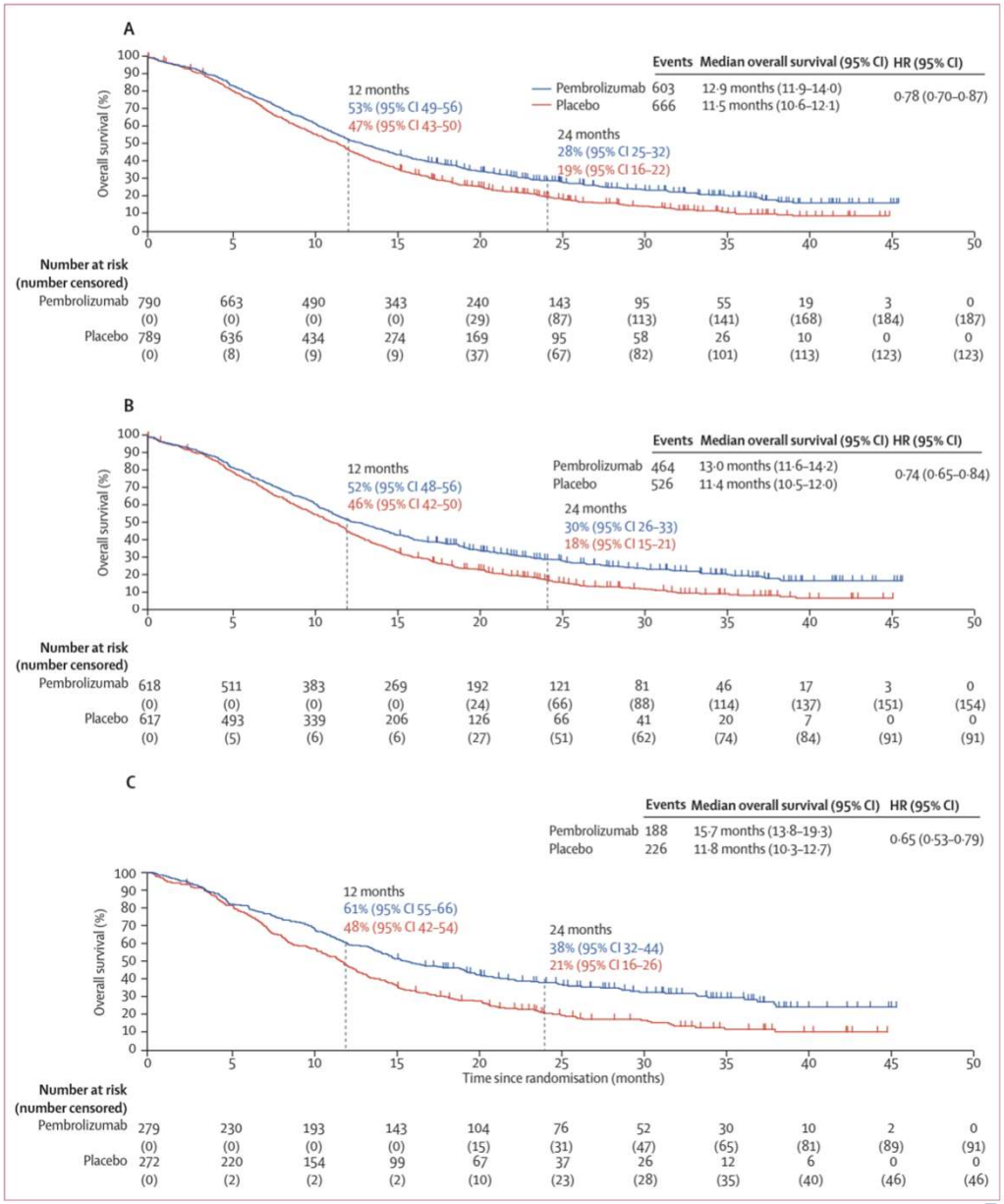
Rha SY, et al. Lancet Oncol. 2023 Nov;24(11):1181-1195. doi: 10.1016/S1470-2045(23)00515-6.



KEYNOTE-859

Amélioration significative de la survie globale

- Population ITT

12,9 mois vs 11,5 (HR=0,78; 95% CI 0,70-0,87)
p<0,0001

- Population PS-PD-L1≥1

13,0 mois vs 11,4 (HR=0,74; 95% CI 0,65–0,84)
p<0,0001

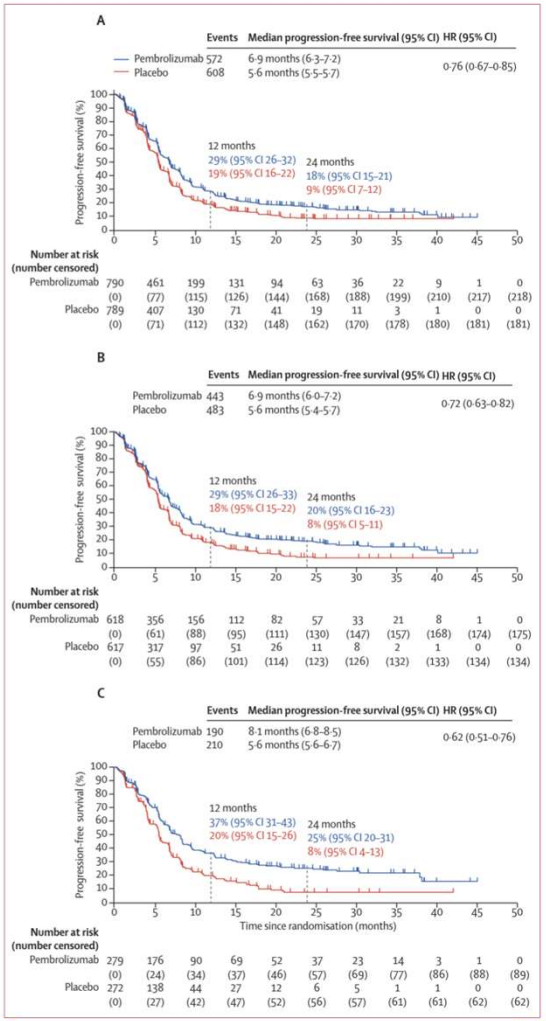
- Population CPS-PD-L1≥10

15,7 mois vs 11,8 (HR=0,65 95% CI 0,53–0,79)
p<0,0001

Rha SY, et al. Lancet Oncol. 2023 Nov;24(11):1181-1195. doi: 10.1016/S1470-2045(23)00515-6.

KEYNOTE-859

PFS médiane		
	Pembro CT	Placebo CT
ITT	6,9	5,6
≥1	6,9	5,6
≥10	8,1	5,6



	PD-L1 CPS ≥10 population		PD-L1 CPS ≥1 population		ITT population	
	Pembrolizumab plus chemotherapy group (n=279)	Placebo plus chemotherapy group (n=272)	Pembrolizumab plus chemotherapy group (n=618)	Placebo plus chemotherapy group (n=617)	Pembrolizumab plus chemotherapy group (n=790)	Placebo plus chemotherapy group (n=789)
Objective response, n (%)	169 (61%)	117 (43%)	322 (52%)	263 (43%)	405 (51%)	331 (42%)
Best response						
Complete response	36 (13%)	14 (5%)	61 (10%)	36 (6%)	75 (9%)	49 (6%)
Partial response	133 (48%)	103 (38%)	261 (42%)	227 (37%)	330 (42%)	282 (36%)
Stable disease†	70 (25%)	105 (39%)	194 (31%)	243 (39%)	256 (32%)	314 (40%)
Progressive disease	24 (9%)	28 (10%)	54 (9%)	64 (10%)	73 (9%)	87 (11%)
Not evaluable‡/not assessed§	16 (6%)	22 (8%)	48 (8%)	47 (8%)	56 (7%)	57 (7%)

Data are n (%).

Rha SY, et al. Lancet Oncol. 2023 Nov;24(11):1181-1195. doi: 10.1016/S1470-2045(23)00515-6.

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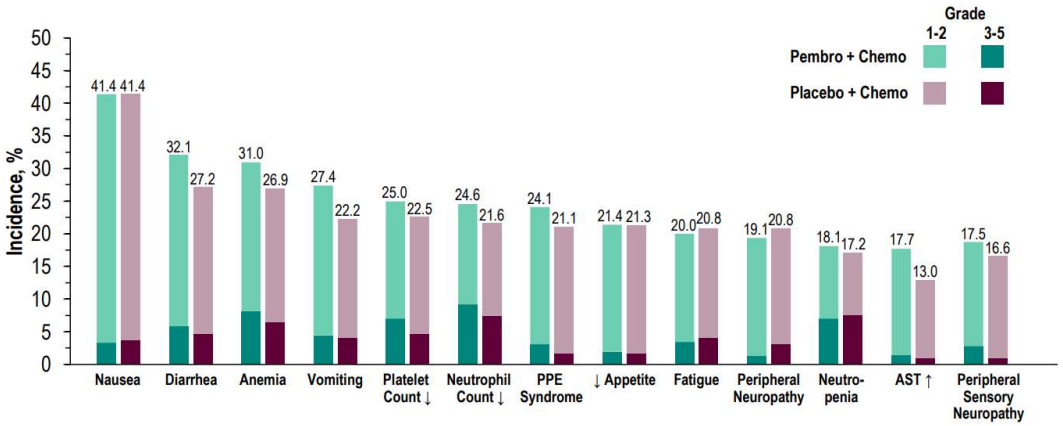
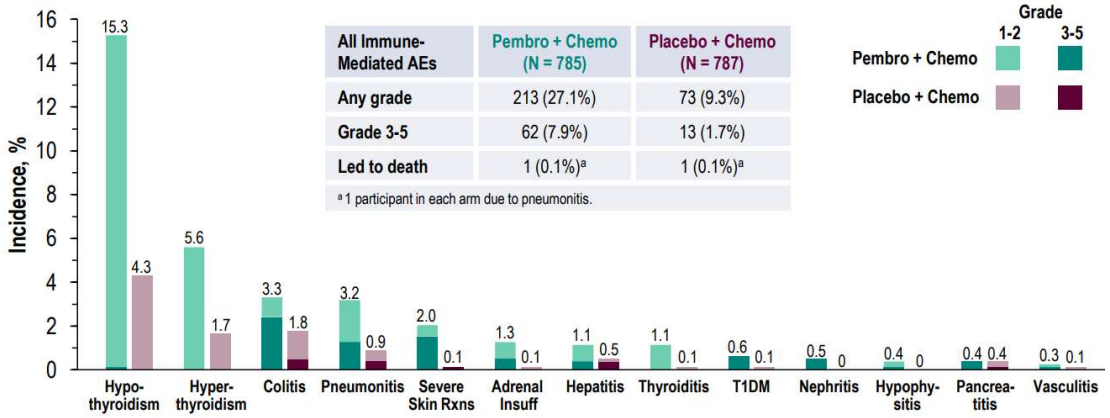
KEYNOTE-859

Treatment-Related Adverse Events, Incidence ≥15%



Immune-Mediated Adverse Events



All Immune-Mediated AEs	Pembro + Chemo (N = 785)	Placebo + Chemo (N = 787)
Any grade	213 (27.1%)	73 (9.3%)
Grade 3-5	62 (7.9%)	13 (1.7%)
Led to death	1 (0.1%)[a]	1 (0.1%)[a]

[a] 1 participant in each arm due to pneumonitis.

	Pembro + Chemo (N = 785)	Placebo + Chemo (N = 787)
Any	751 (95.7%)	736 (93.5%)
Grade 3-5	466 (59.4%)	402 (51.1%)
Led to death	8 (1.0%)[a]	16 (2.0%)[b]
Serious	184 (23.4%)	146 (18.6%)
Led to treatment discontinuation	207 (26.4%)	158 (20.1%)

[a] 1 participant each due to diarrhea, peripheral embolism, pneumonitis, pulmonary hemorrhage, sepsis, septic shock, thrombotic thrombocytopenic purpura, and death (cause unknown).
[b] 3 participants due to septic shock, 2 participants due to acute myocardial infarction, and 1 participant each due to diarrhea, pneumonitis, sepsis, cerebral hemorrhage, cerebrovascular accident, gastric perforation, hepatic function abnormal, neurotoxicity, pulmonary embolism, sudden death, and urosepsis.

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KEYNOTE-859

- **13 Oct. 2023 : avis positif EMA CHMP pour l'utilisation du PEMBROLIZUMAB en combinaison à la CT** en 1ère ligne métastatique dans les adénocarcinomes gastriques, de la jonction œsogastrique et de l'œsophage, HER2 négatifs, avec un **CPS-PD-L1 ≥1**.

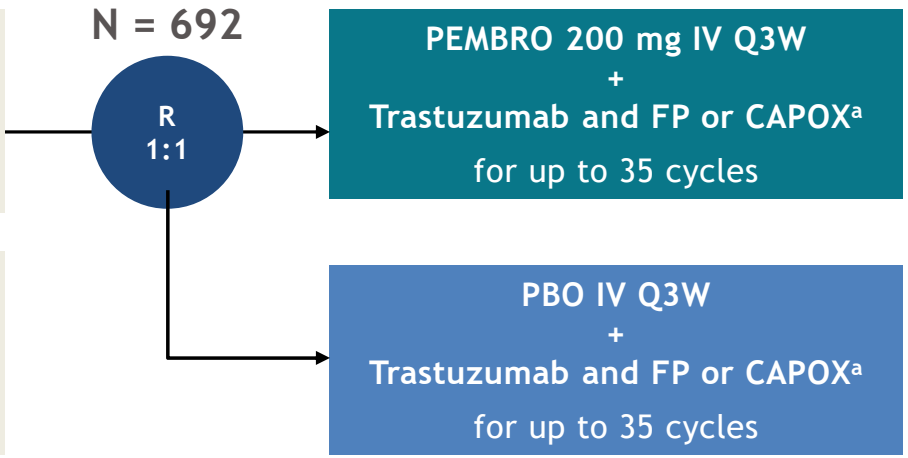
→ remboursement en France en attente.

KEYNOTE-811

Etude de phase III randomisée, 1ère ligne
Estomac-Jonction **HER2 pos.**

Patients:
- Advanced G/GEJ adenocarcinoma
- No prior therapy in advanced setting
- *HER2*-positive

Stratification factors:
- Geographic region
- PD-L1 CPS
- Chemotherapy choice



Dual primary endpoints:
- OS
- PFS

Secondary endpoints:
- ORR
- DOR
- Safety

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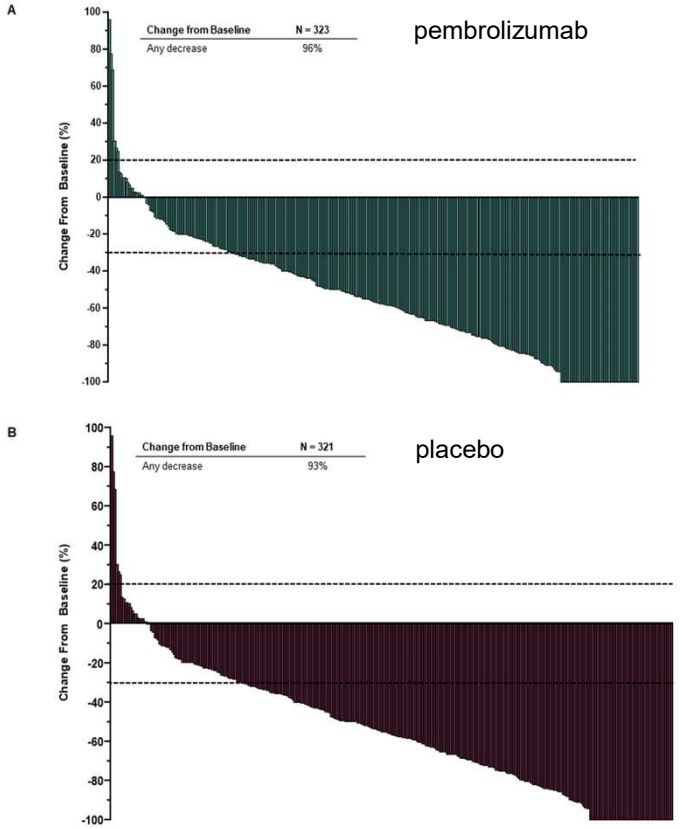
Janjigian YY et al. Nature. 2021;600:727-730.
Janjigian YY, et al. Lancet. 2023 Oct 19:S0140-6736(23)02033-0. doi: 10.1016/S0140-6736(23)02033-0.

KEYNOTE-811

Amélioration significative du taux de réponse

	Intention-to-treat population		PD-L1 CPS ≥1		PD-L1 CPS <1	
IA3	**Pembrolizumab Group N = 350**	**Placebo Group N = 348**	**Pembrolizumab Group N = 298**	**Placebo Group N = 296**	**Pembrolizumab Group N = 52**	**Placebo Group N = 52**
Objective response rate, n	254	209	218	173	36	36
% (95% CI)	72.6 (67.6-77.2)	60.1 (54.7-65.2)	73.2 (67.7-78.1)	58.4 (52.6-64.1)	69.2 (54.9-81.3)	69.2 (54.9-81.3)
Best response, n (%)						
Complete response	58 (16.6)	39 (11.2)	49 (16.4)	30 (10.1)	9 (17.3)	9 (17.3)
Partial response	196 (56.0)	170 (48.9)	169 (56.7)	143 (48.3)	27 (51.9)	27 (51.9)
Stable disease	67 (19.1)	95 (27.3)	55 (18.5)	83 (28.0)	12 (23.1)	12 (23.1)
Disease control rate, n (%)	321 (91.7)	304 (87.4)	273 (91.6)	256 (86.5)	48 (92.3)	48 (92.3)
Mean time to response (SD), months	1.9 (1.3)	1.9 (1.0)	1.8 (1.3)	1.9 (1.0)	2.0 (1.2)	2.1 (1.2)
Median duration of response (95% CI), months	11.3 (9.8-12.7)	9.5 (7.2-11.2)	11.3 (9.9-13.7)	9.6 (7.1-11.2)	9.8 (7.4-17.3)	8.5 (6.9-16.9)
Response duration of ≥24 months, %	30	18	30	18	25	21

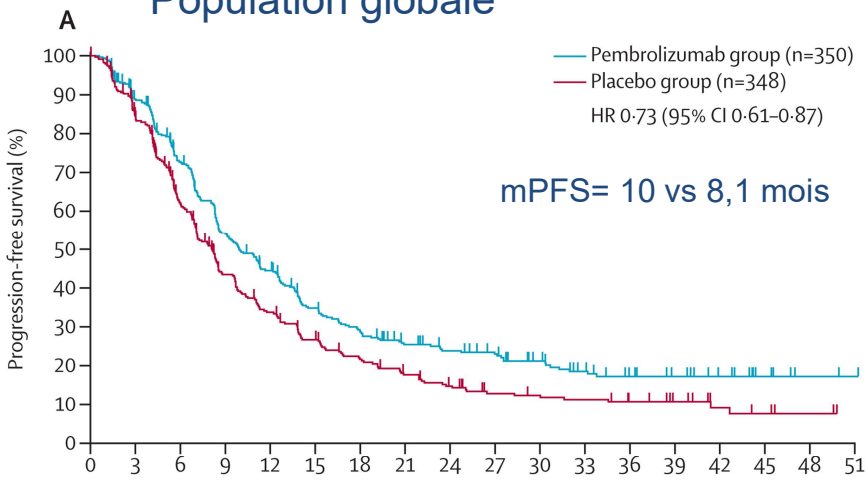


Janjigian YY et al. Nature. 2021;600:727-730.
Janjigian YY et al. Oral presentation at ASCO; June 4–8, 2021; Virtual. Abstract 4013

KEYNOTE-811

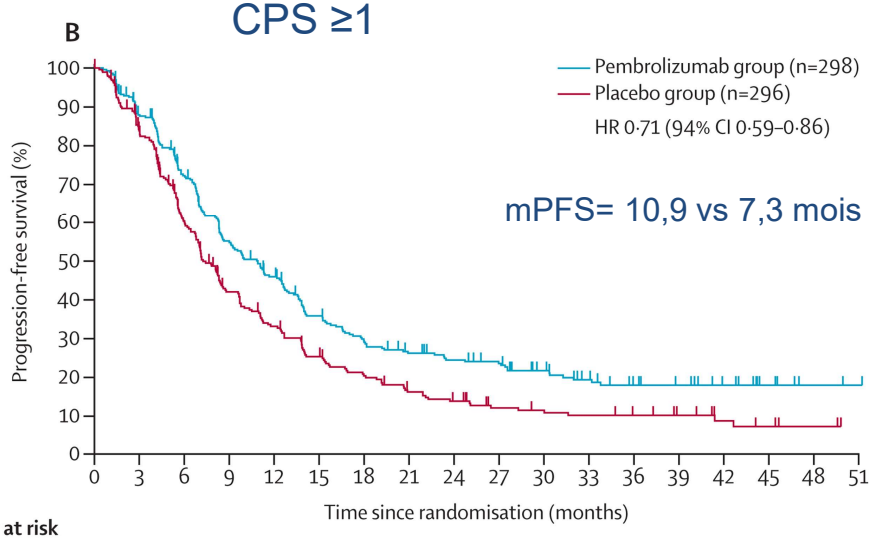
Amélioration significative de la survie sans progression (3è analyse interm.)*

Population globale



Number at risk (number censored)																	
Pembrolizumab group	350	296	234	173	139	102	84	67	59	53	41	31	24	20	14	6	2	1
	(0)	(16)	(25)	(28)	(31)	(39)	(40)	(47)	(51)	(55)	(63)	(68)	(73)	(77)	(83)	(91)	(85)	(96)
Placebo group	348	274	184	121	93	71	55	43	34	25	23	21	17	11	6	4	2	0
	(0)	(22)	(43)	(52)	(53)	(56)	(59)	(61)	(63)	(68)	(69)	(69)	(72)	(78)	(82)	(83)	(85)	(87)

CPS ≥1



Number at risk (number censored)																		
Pembrolizumab group	298	250	200	151	123	91	74	63	56	51	39	30	23	20	14	6	2	1
	(0)	(13)	(19)	(21)	(24)	(30)	(31)	(34)	(37)	(40)	(48)	(53)	(58)	(61)	(67)	(75)	(79)	(80)
Placebo group	296	231	152	100	78	58	45	34	28	20	18	16	14	10	6	4	2	0
	(0)	(19)	(36)	(43)	(44)	(46)	(48)	(50)	(51)	(56)	(57)	(57)	(59)	(63)	(66)	(67)	(69)	(71)

* P=0,0002 à la 2nde analyse intermédiaire

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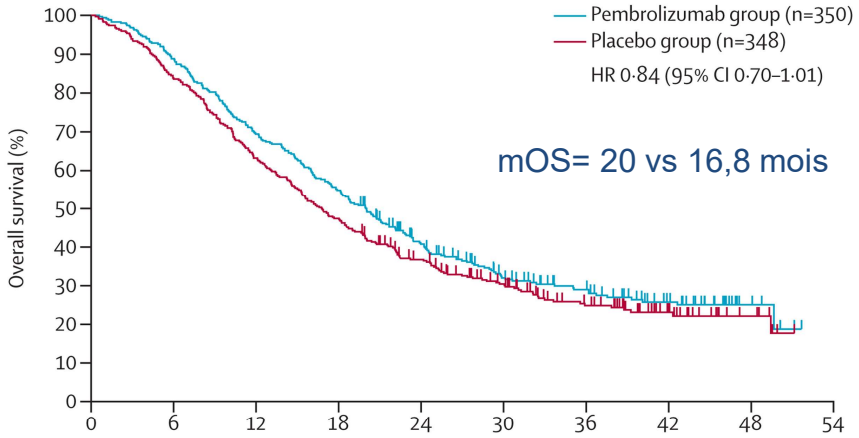
Janjigian YY et al. Nature. 2021;600:727-730.
Janjigian YY, et al. Lancet. 2023 Oct 19:S0140-6736(23)02033-0. doi: 10.1016/S0140-6736(23)02033-0.

KEYNOTE-811

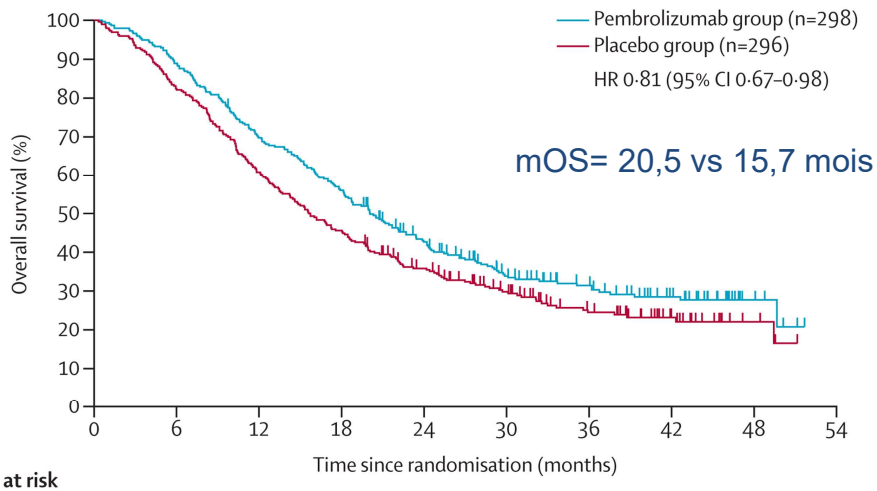
Pas d'amélioration significative de la survie globale (3è analyse interm.)*

A Population globale



Number at risk (number censored)										
Pembrolizumab group	350 (0)	311 (0)	243 (0)	192 (0)	126 (19)	84 (36)	61 (52)	37 (70)	7 (99)	0 (105)
Placebo group	348 (0)	292 (0)	220 (0)	165 (0)	116 (13)	83 (27)	51 (46)	25 (69)	8 (85)	0 (92)

B CPS ≥1



Number at risk (number censored)										
Pembrolizumab group	298 (0)	265 (0)	207 (0)	166 (0)	115 (13)	78 (28)	58 (43)	37 (59)	7 (88)	0 (94)
Placebo group	296 (0)	244 (0)	180 (0)	135 (0)	96 (11)	67 (25)	41 (41)	21 (59)	5 (74)	0 (78)

* NS à la 1ère analyse mais données non matures

Janjigian YY et al. Nature. 2021;600:727-730.
Janjigian YY, et al. Lancet. 2023 Oct 19:S0140-6736(23)02033-0. doi: 10.1016/S0140-6736(23)02033-0.

KEYNOTE-811

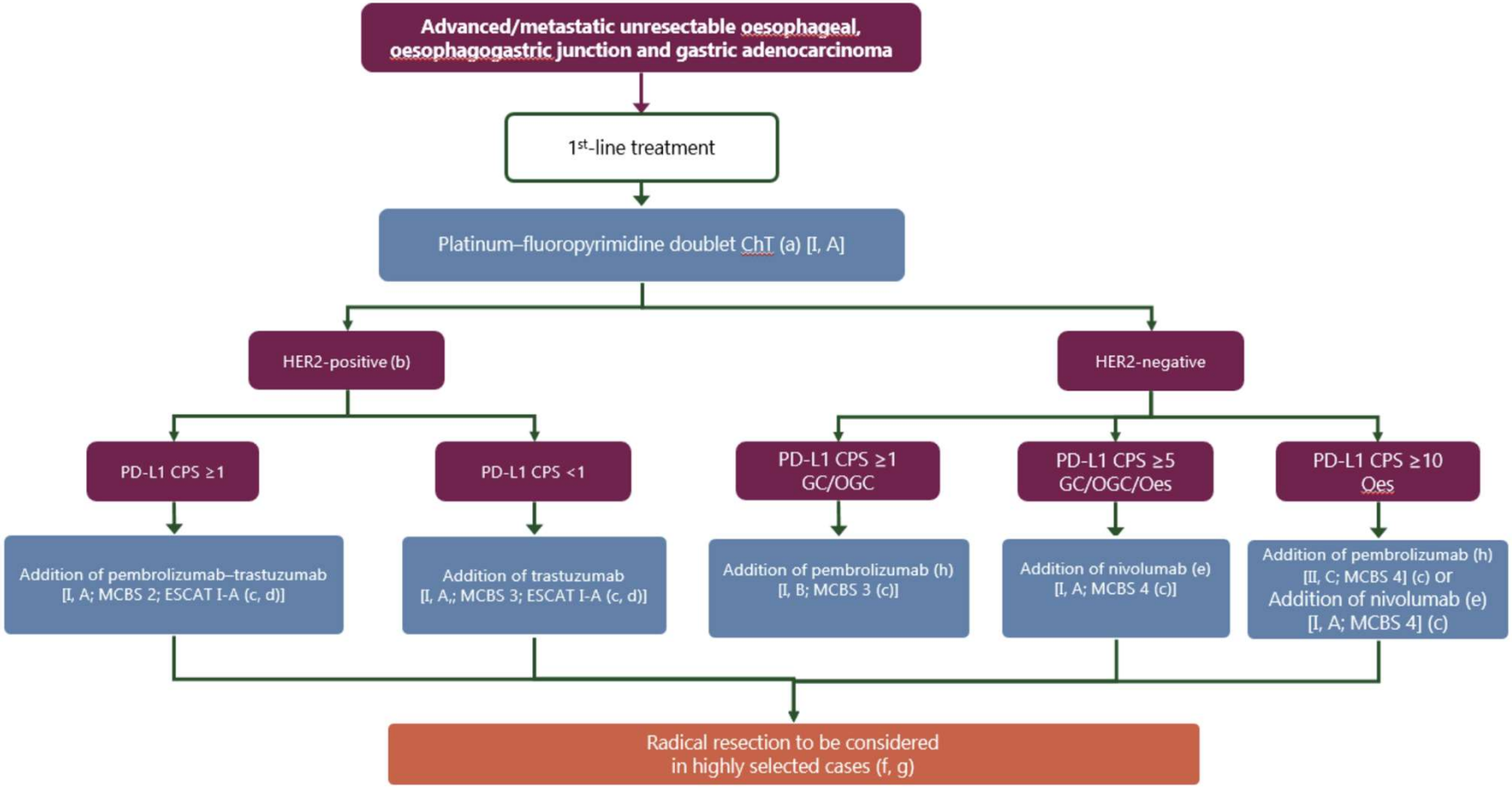
- Amélioration de la **survie globale** et **sans progression** et du taux de réponse dans le **sous-groupe CPS-PD-L1≥1** avec la combinaison **PEMBROLIZUMAB+TRASTUZUMAB+CT.**

- **Tolérance :** pas de signal de toxicité particulier

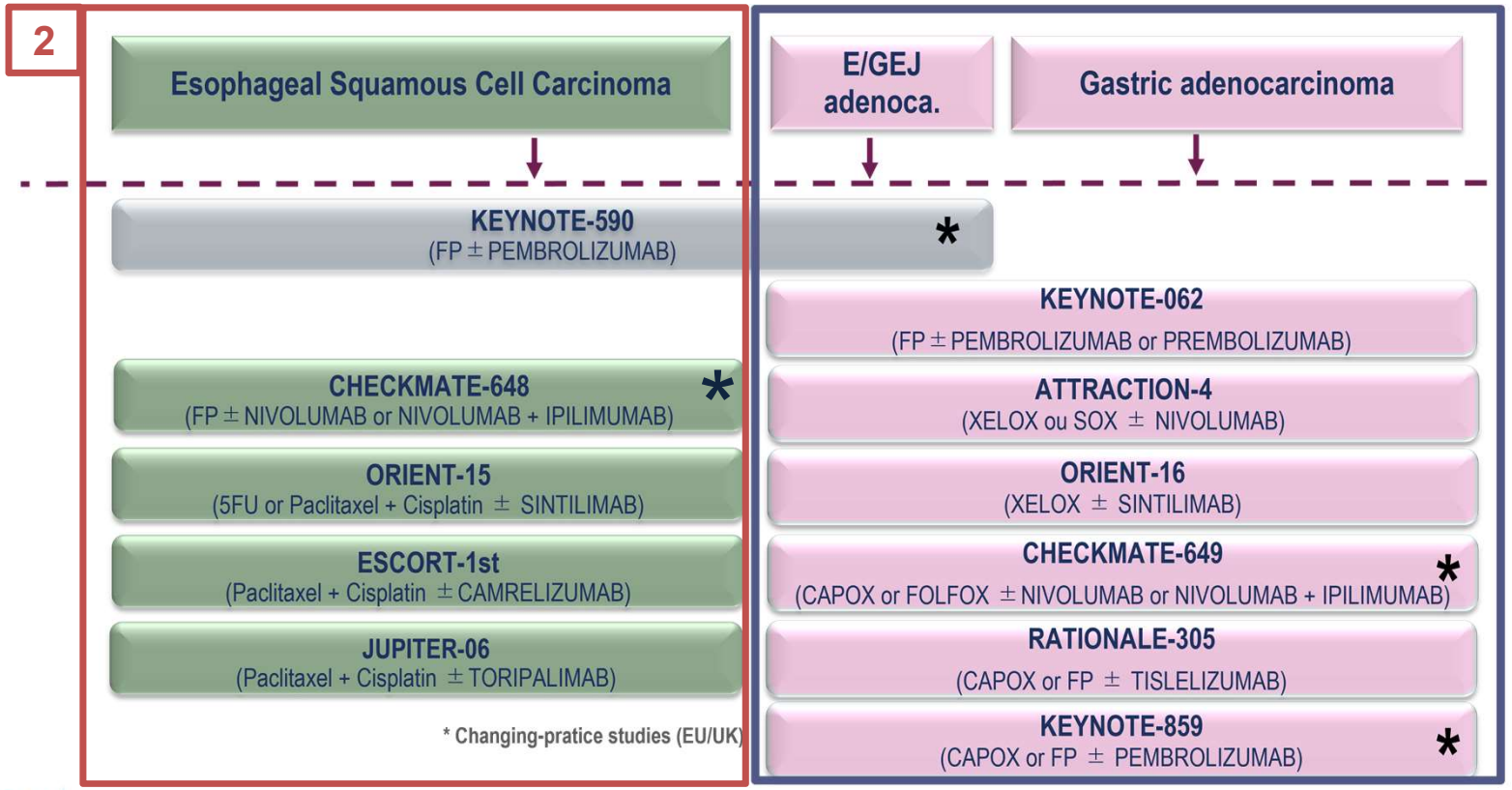
- **Accord EMA juillet 2023** → remboursement en France en attente.

Janjigian YY et al. Nature. 2021;600:727-730.
Janjigian YY, et al. Lancet. 2023 Oct 19:S0140-6736(23)02033-0. doi: 10.1016/S0140-6736(23)02033-0.

Actualisation des guidelines ESMO



Immunothérapie dans les cancers œsogastriques avancés

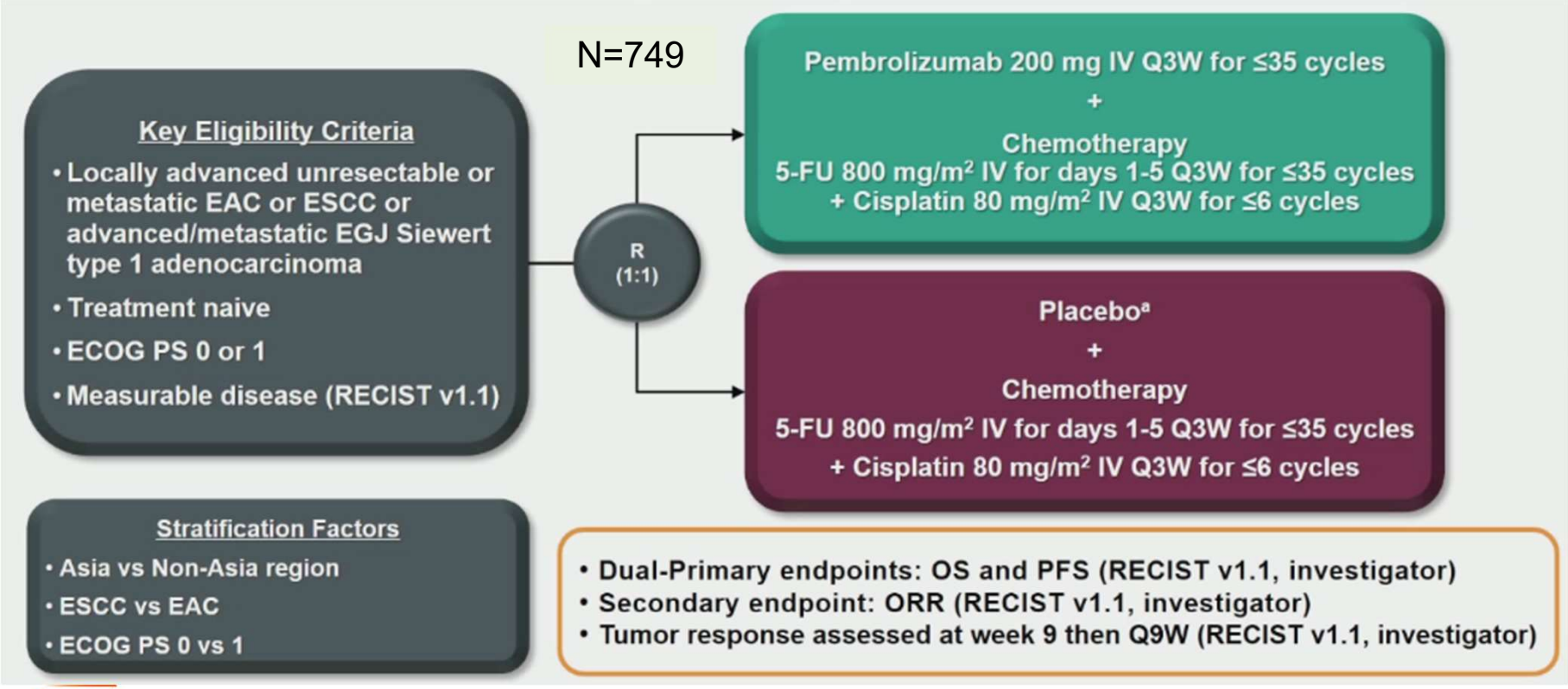


KEYNOTE-590

Etude de phase III randomisée, 1ère ligne

Œsophages (ADK + CE)

JOG (ADK HER2nég.; Siewert I)



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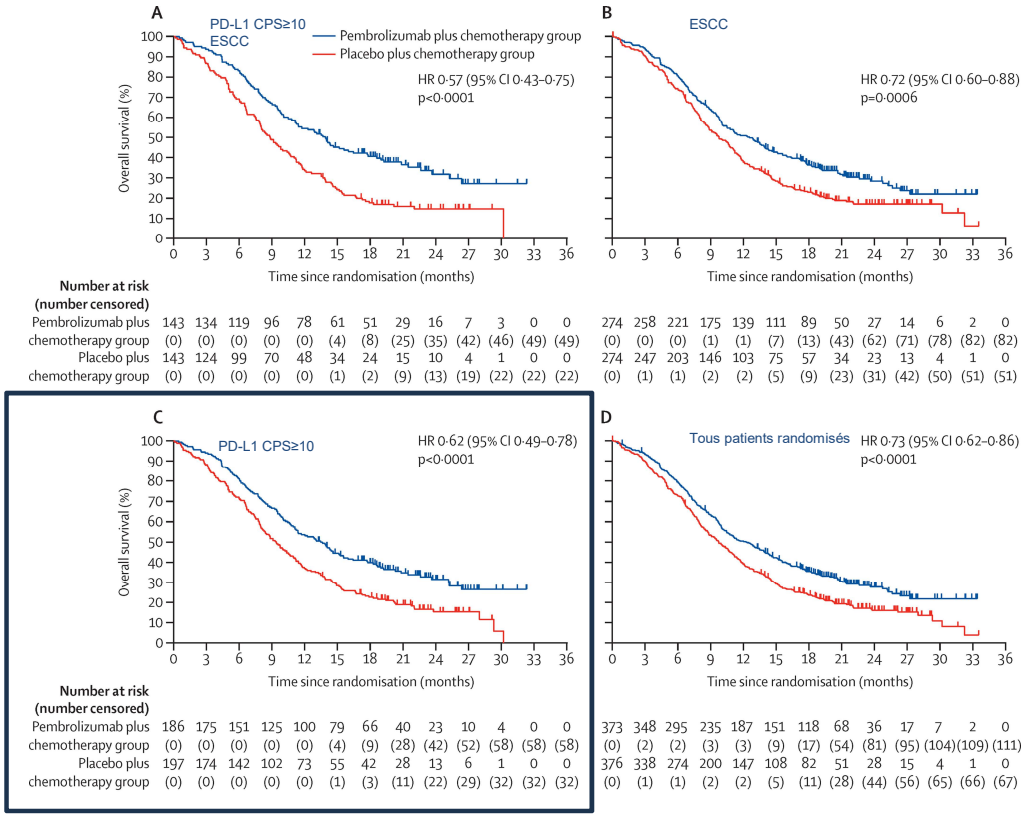
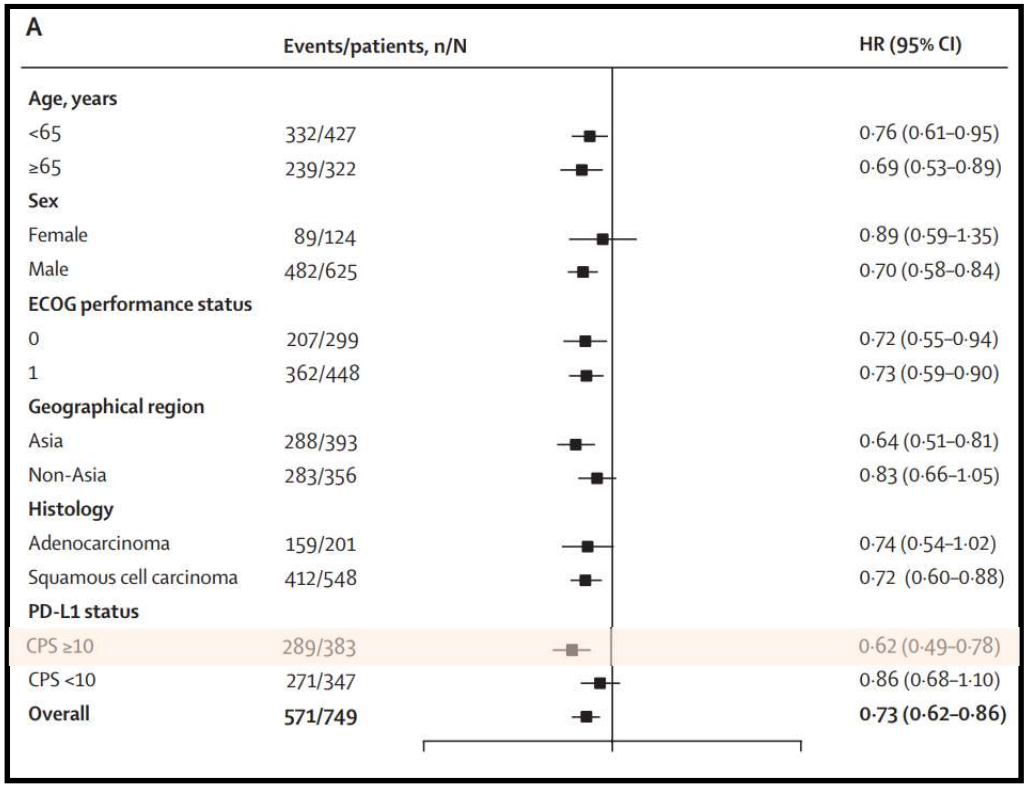
JM Sun et al, Lancet 2021; 398: 759–71

KEYNOTE-590





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JM Sun et al, Lancet 2021; 398: 759–71

KEYNOTE-590

- **Juillet 2021** : AMM européenne pour le **pembrolizumab** en association à la chimiothérapie de première ligne dans les cancers de l'œsophage avancé (CE ou ADK de la JOG (Siewert I) HER2 négatifs) avec un score d'expression de **PD-L1 CPS ≥10**.

- **Mars 2022** : accès précoce

- **Juillet 2023 : JO+**

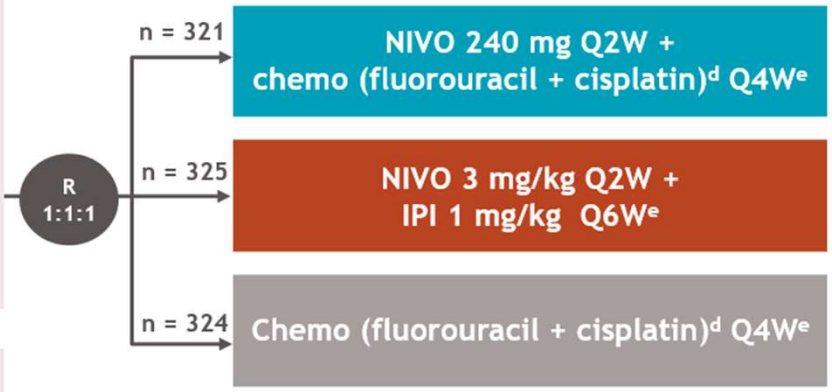
JM Sun et al, Lancet 2021; 398: 759–71

CHECKMATE-648

Carcinomes épidermoïdes œsophage

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



N=970 patients

Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

- 680 (70%) des patients d'origine asiatique
- 473 (49%) TPS PD-L1 ≥1%

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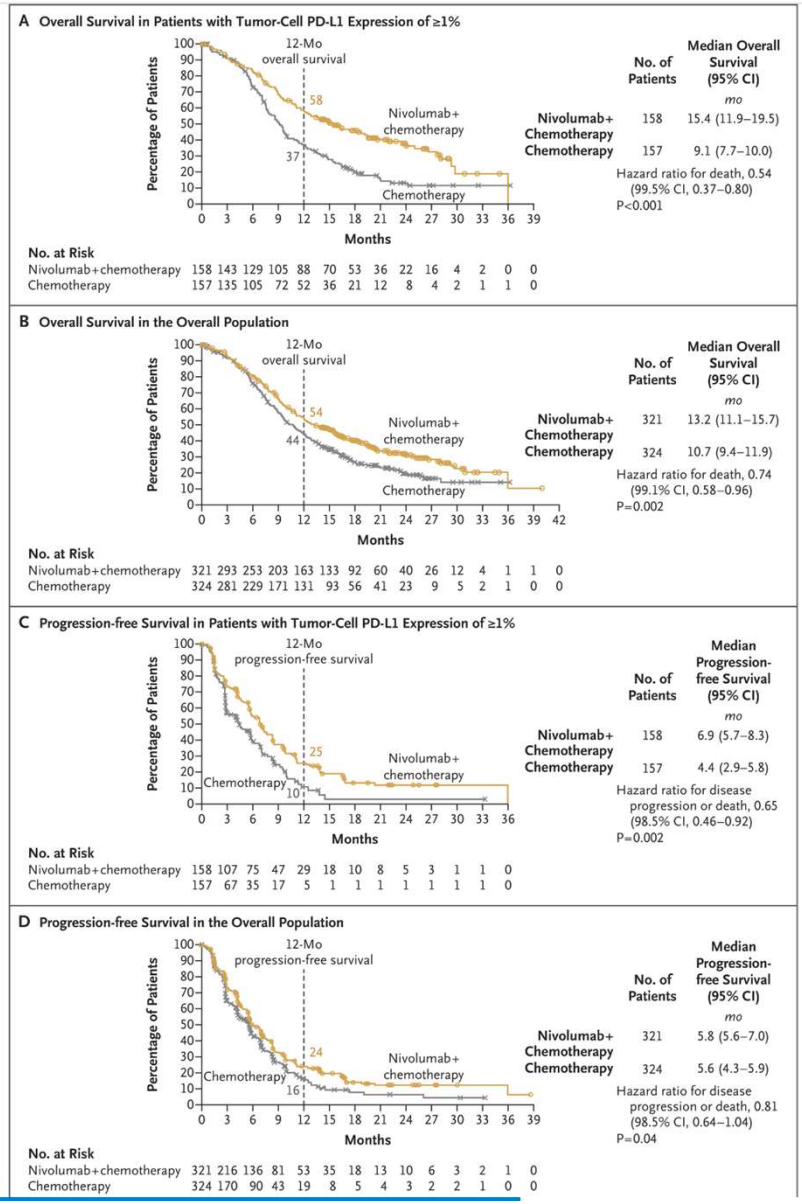
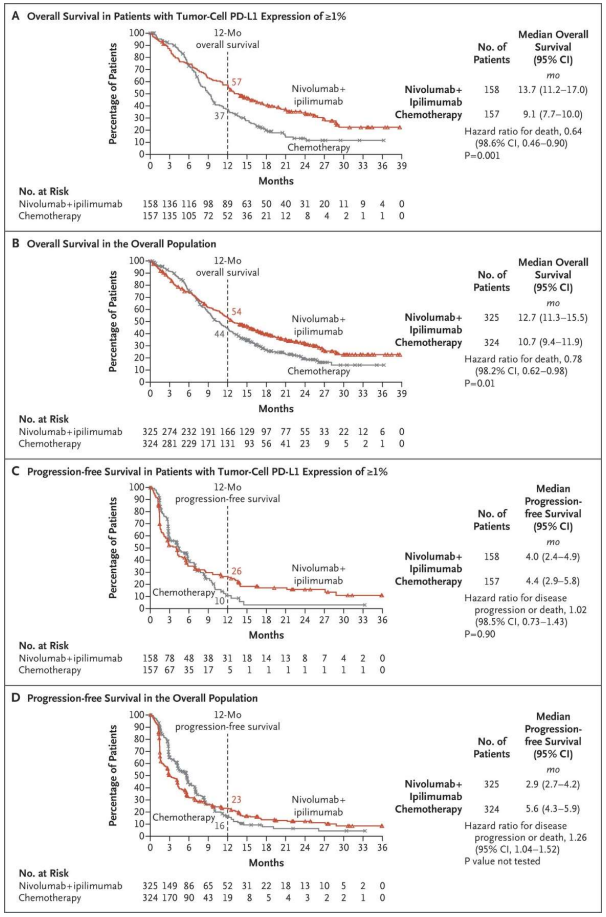
Doki Y, et al. N Engl J Med. 2022 Feb 3;386(5):449-462. doi: 10.1056/NEJMoa2111380.

CHECKMATE-648

NIVO + CHIMIO



NIVO + IPI



- Bénéfice en SG de l'association nivolumab + chimio et de la double immunothérapie nivo+ ipi chez les patients avec CE de l'œsophage PDL1 ≥ 1 %.
- Pas de bénéfice en SSP de la double immuno.

Doki Y, et al. N Engl J Med. 2022 Feb 3;386(5):449-462. doi: 10.1056/NEJMoa2111380.

CHECKMATE-648

Table 2. Antitumor Activity, as Assessed by Blinded Independent Central Review.*

Variable	Patients with Tumor-Cell PD-L1 Expression of ≥1%			Overall Population		
	Nivolumab plus Chemotherapy (N=158)	Nivolumab plus Ipilimumab (N=158)	Chemotherapy (N=157)	Nivolumab plus Chemotherapy (N=321)	Nivolumab plus Ipilimumab (N=325)	Chemotherapy (N=324)
Objective response rate						
No. of patients (%)	84 (53)	56 (35)	31 (20)	152 (47)	90 (28)	87 (27)
95% CI	45–61	28–43	14–27	42–53	23–33	22–32
Best overall response — no. (%)						
Complete response	26 (16)	28 (18)	8 (5)	43 (13)	36 (11)	20 (6)
Partial response	58 (37)	28 (18)	23 (15)	109 (34)	54 (17)	67 (21)
Stable disease	40 (25)	43 (27)	72 (46)	103 (32)	103 (32)	148 (46)
Progressive disease	22 (14)	48 (30)	24 (15)	42 (13)	103 (32)	38 (12)
Could not be evaluated	12 (8)	11 (7)	30 (19)	24 (7)	29 (9)	51 (16)
Median time to response (range) — mo†	1.5 (0.6–4.3)	1.5 (1.2–8.4)	1.5 (1.3–9.7)	1.5 (0.6–6.8)	1.5 (1.2–8.4)	1.5 (1.1–9.7)
Median duration of response (95% CI) — mo†	8.4 (6.9–12.4)	11.8 (7.1–27.4)	5.7 (4.4–8.7)	8.2 (6.9–9.7)	11.1 (8.3–14.0)	7.1 (5.7–8.2)
Patients with ongoing response — no. (%)†	11 (13)	14 (25)	1 (3)	26 (17)	20 (22)	5 (6)

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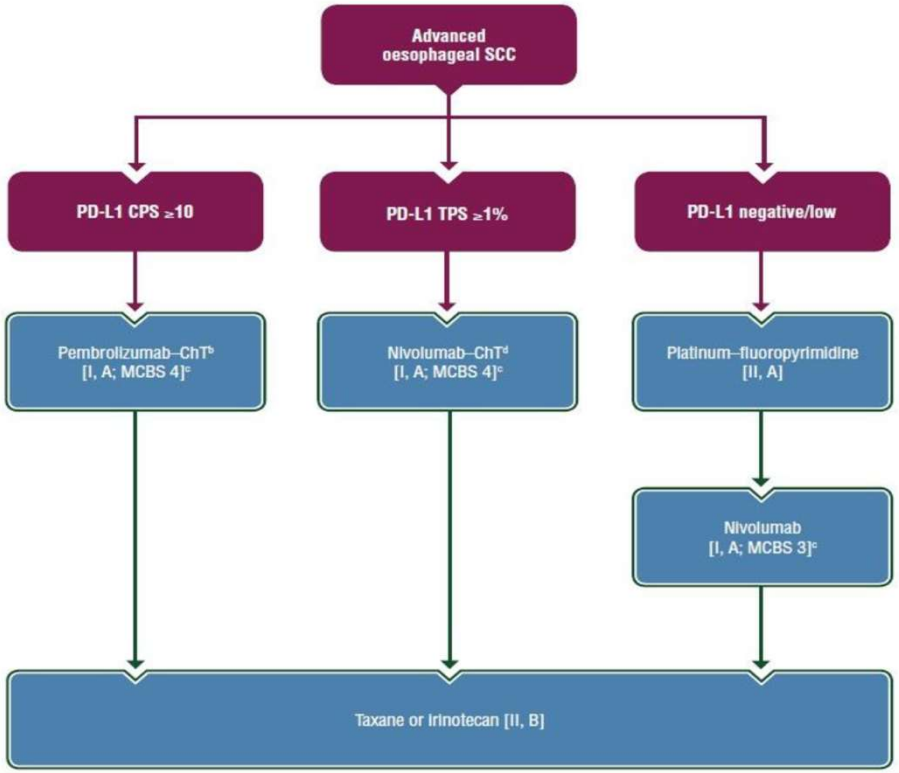
Doki Y, et al. N Engl J Med. 2022 Feb 3;386(5):449-462. doi: 10.1056/NEJMoa2111380.

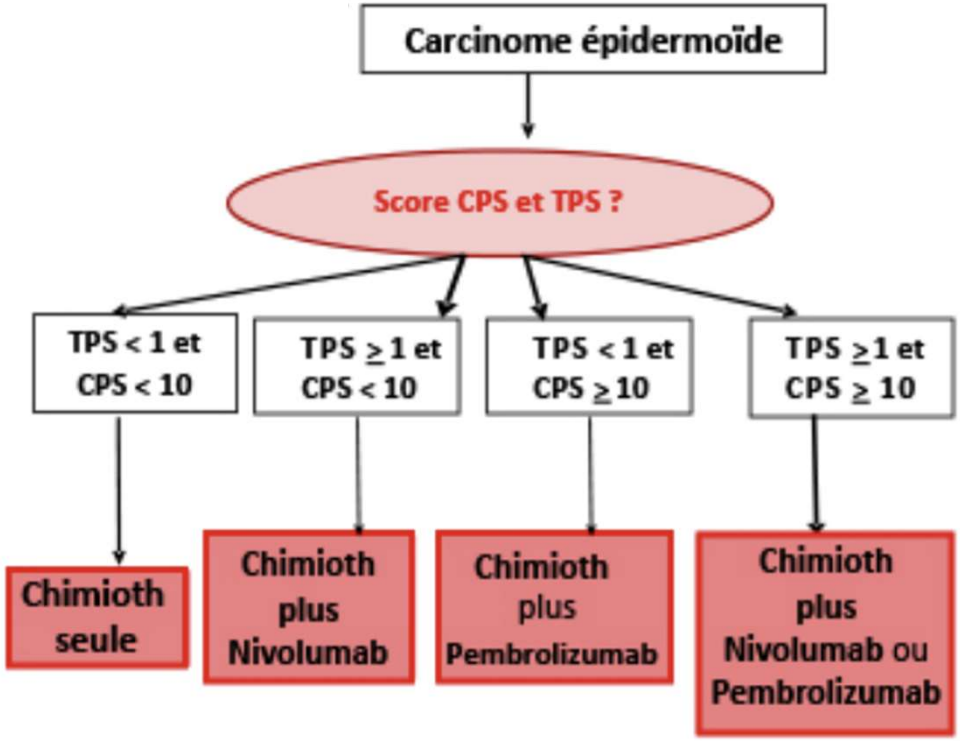
Conclusion œsophage

- **Mai 2021** : accord EMA pour **pembrolizumab** + chimio chez les patients avec cancer de l'œsophage ou de la JOG (SI, HER2 neg) avec **CPS-PD-L1≥10** (JO+).

- **Mars 2022** : accord EMA pour **nivolumab** chez les patients avec un CE de l'œsophage avancé et un **TPS-PDL1≥1%**
  - Nivolumab + chimiothérapie (JO+)
  - Nivolumab + ipilimumab (non remboursable en France)

Guidelines





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Obermannová R et al. Annals of Oncology. 2022 Online
Veziant J, et al. Dig Liver Dis. 2023

2 - Cancers hépato-biliaires

Cholangiocarcinomes

Carcinomes hépato-cellulaires

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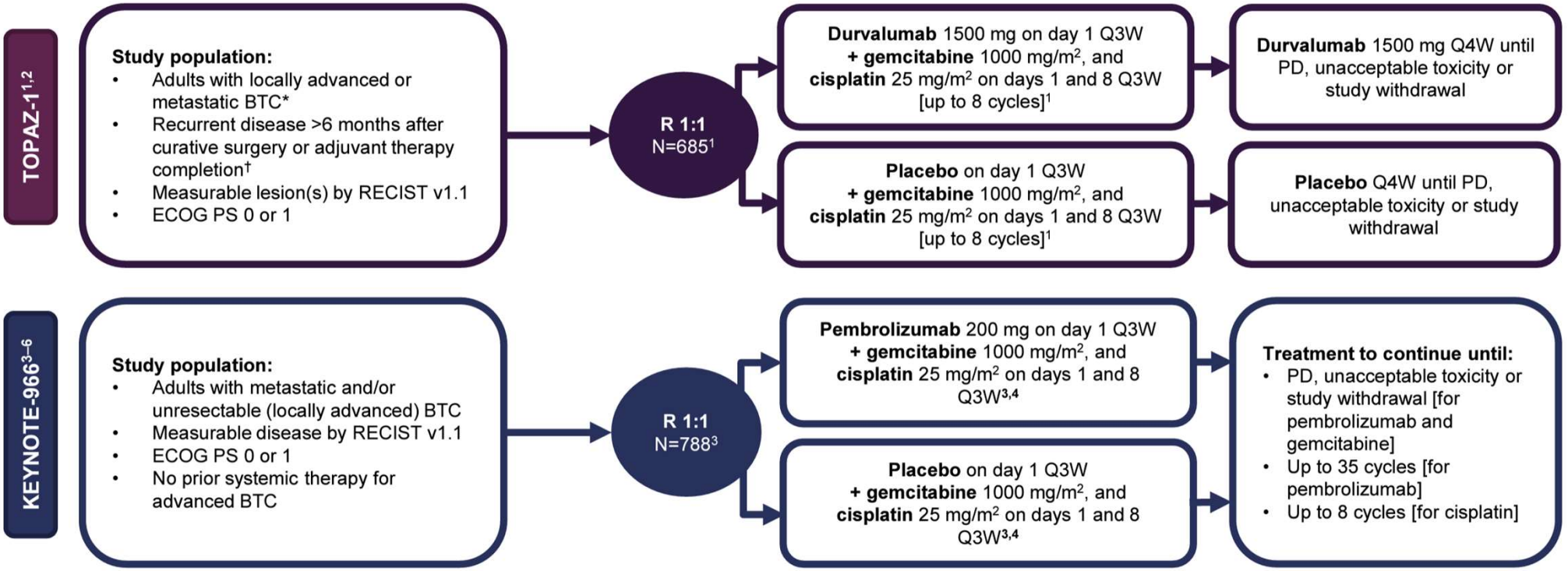
Immuno / voies biliaires

2 études en 1ère ligne



Do-YounOh, NEJM Evid 2022; 1 (8), DOI:10.1056/EVIDoa2200015

Kelley RK, et al. Lancet. 2023 Jun 3;401(10391):1853-1865.

Immuno / voies biliaires

NEJM Evidence

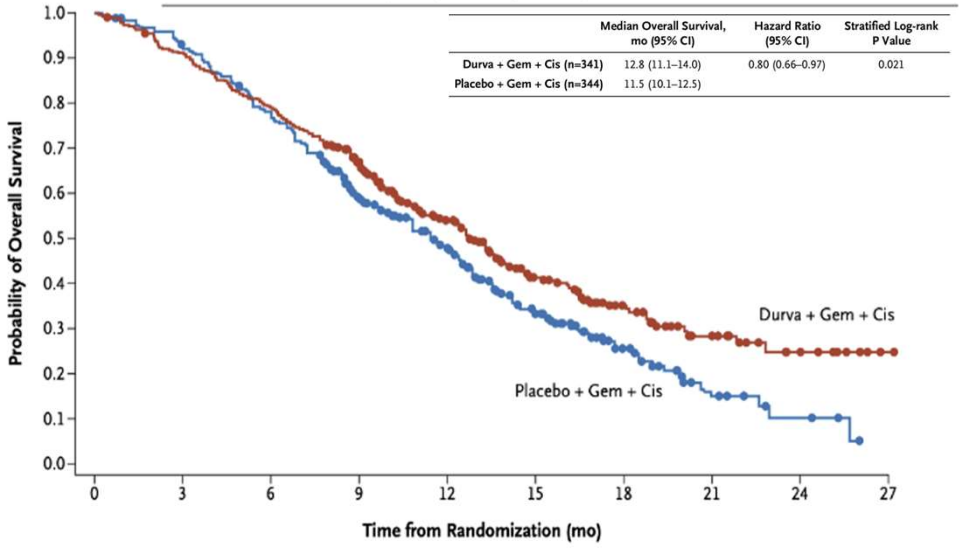
TOPAZ-1

Published June 1, 2022
NEJM Evid 2022; 1 (8)
DOI: 10.1056/EVIDoa2200015

ORIGINAL ARTICLE

Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer

Do-Youn Oh, M.D., Ph.D.,[1] Aiwu Ruth He, M.D., Ph.D.,[2] Shukui Qin, M.D.,[3] Li-Tzong Chen, M.D., Ph.D.,[4,5,6] Takuji Okusaka, M.D., Ph.D.,[7] Arndt Vogel, M.D.,[8] Jin Won Kim, M.D., Ph.D.,[9] Thatthan Suksombooncharoen, M.D.,[10] Myung Ah Lee, M.D., Ph.D.,[11] Masayuki Kitano, M.D., Ph.D.,[12] Howard Burris, M.D.,[13] Mohamed Bouattour, M.D.,[14] Suebpong Tanasanvimon, M.D.,[15] Mairéad G. McNamara, M.B., Ph.D.,[16] Renata Zaucha, M.D., Ph.D.,[17] Antonio Avallone, M.D.,[18] Benjamin Tan, M.D.,[19] Juan Cundom, M.D.,[20] Choong-kun Lee, M.D., Ph.D.,[21] Hidenori Takahashi, M.D., Ph.D.,[22] Masafumi Ikeda, M.D., Ph.D.,[23] Jen-Shi Chen, M.D.,[24] Julie Wang, Ph.D.,[25] Mallory Makowsky, Pharm.D.,[25] Nang Rokutanda, M.D., Ph.D.,[25] Philip He, Ph.D.,[25,26] John F. Kurland, Ph.D.,[25] Gordon Cohen, M.D., M.P.H.,[25] and Juan W. Valle, M.D.,[16] for the TOPAZ-1 Investigators*



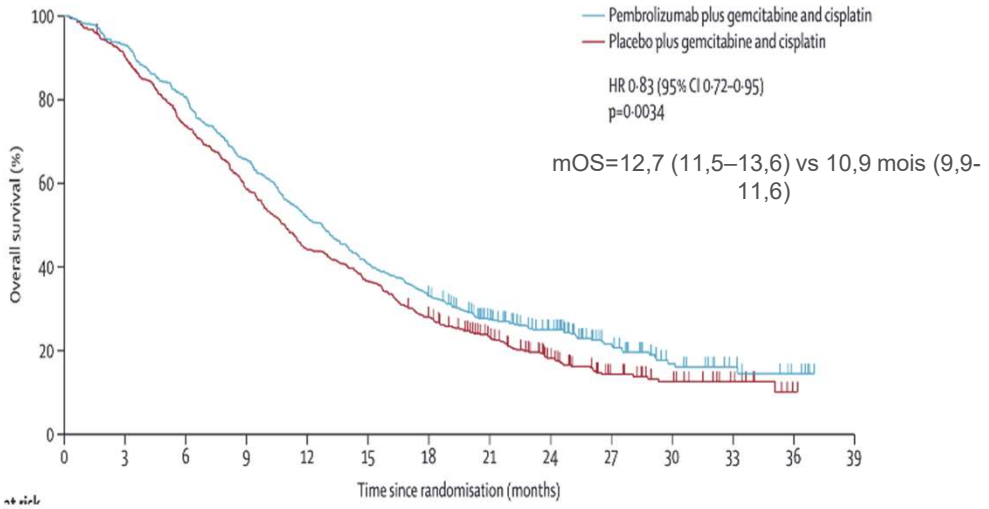
	Median Overall Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value
Durva + Gem + Cis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + Gem + Cis (n=344)	11.5 (10.1–12.5)		

ORR: 26.7% vs 18.7%

Do-YounOh, NEJM Evid 2022; 1 (8), DOI:10.1056/EVIDoa2200015

Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial

Robin Kate Kelley, Makoto Ueno*, Changhoon Yoo, Richard S Finn, Junji Furuse, Zhenggang Ren, Thomas Yau, Heinz-Josef Klümpen, Stephen L Chan, Masato Ozaka, Chris Verslype, Mohamed Bouattour, Joon Oh Park, Olga Barajas, Uwe Pelzer, Juan W Valle, Li Yu, Usha Malhotra, Abby B Siegel, Julien Edeline, Arndt Vogel*, on behalf of the KEYNOTE-966 Investigators†*



mOS=12,7 (11,5–13,6) vs 10,9 mois (9,9-11,6)

ORR: 29% vs 29%

Kelley RK, et al. Lancet. 2023 Jun 3;401(10391):1853-1865.

Immuno / voies biliaires

DURVALUMAB

- Avis positif EMA CHMP 10 Nov. 2022
- Autorisation d'accès précoce le 22/09/22
- **PUT-RD en cours.**

PEMBROLIZUMAB

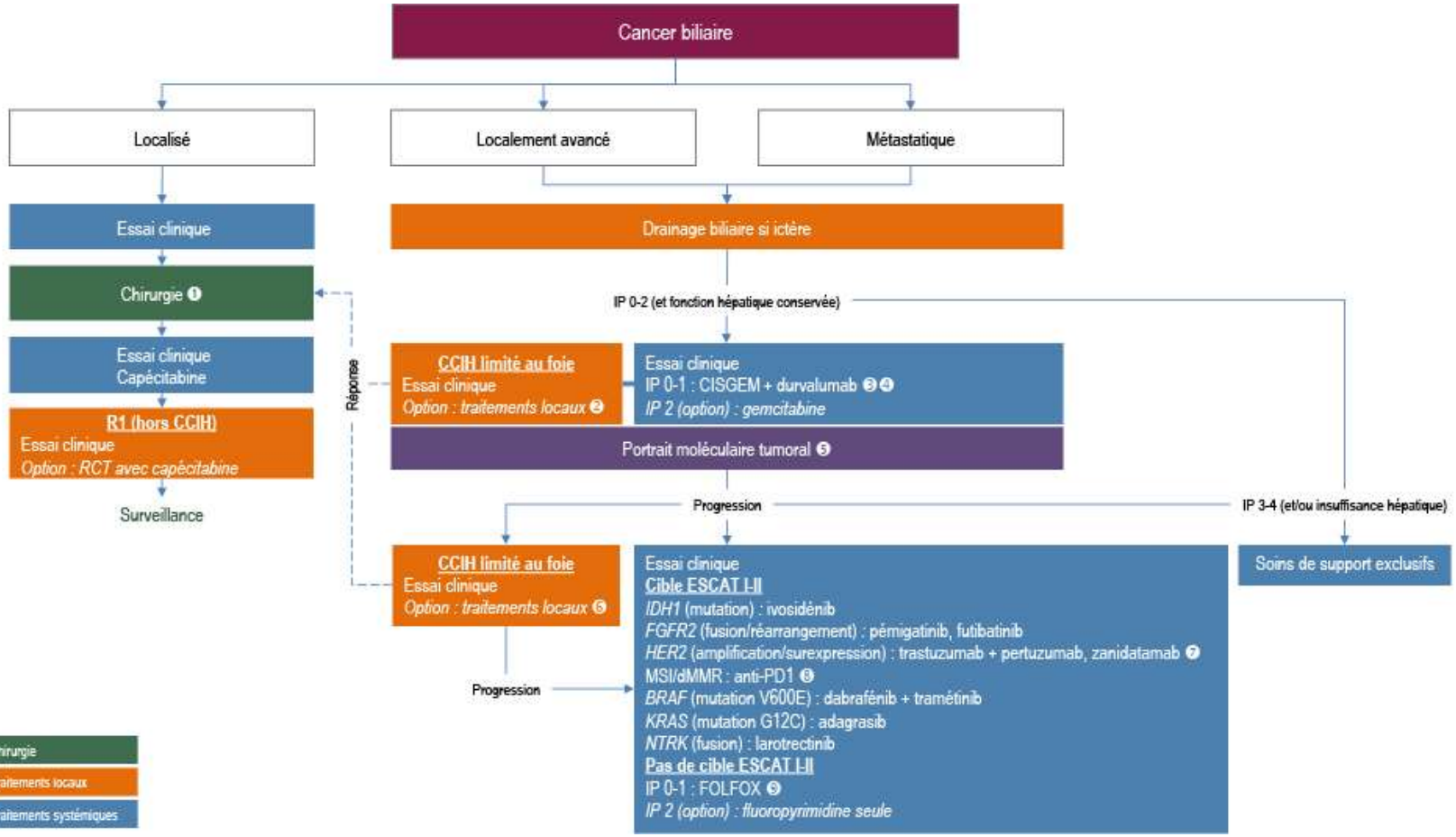
Avis positif EMA CHMP 10 Nov. 2023

MERCK

Media > News releases > News release

Merck Receives Positive EU CHMP Opinion for KEYTRUDA® (pembrolizumab) Plus Gemcitabine and Cisplatin as First-Line Treatment for Locally Advanced Unresectable or Metastatic Biliary Tract Cancer

Guidelines voies biliaires



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Malka D, TNCD 2023

2 - Cancers hépato-biliaires

Cholangiocarcinomes

Carcinomes hépato-cellulaires

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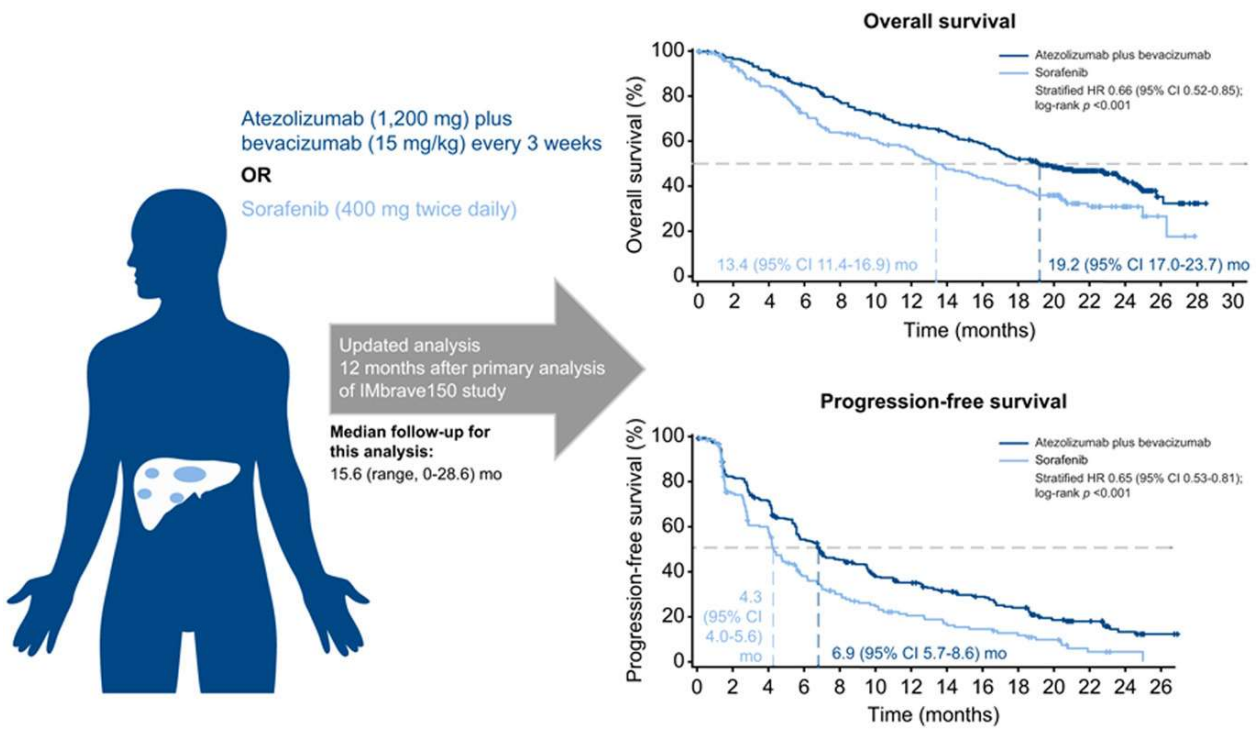
Immuno / CHC

IMbrave150: Atezolizumab plus bevacizumab versus sorafenib in patients with unresectable HCC



Atezolizumab + Bevacizumab
Nouveau SOC en L1

Résultats (update 2022)

- **OS 19.2 mois** vs 13.4 mois
  (HR=0,66; 95% CI 0.52-0.85; p <0.001)
- **PFS 6.9 mois** vs 4.3 mois
  (HR=0,65; 95% CI 0.53-0.81; p <0.001)
- **ORR 30%** vs 11%

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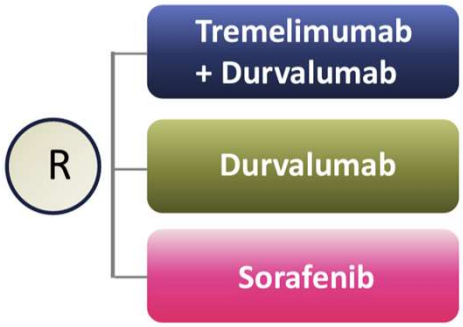
Finn RS, et alN Engl J Med. 2020 May 14;382(20):1894-1905. doi: 10.1056/NEJMoa1915745.
Cheng AL, et al. J Hepatol. 2022 Apr;76(4):862-873. doi: 10.1016/j.jhep.2021.11.030.

ATEZO-BEVA CHC

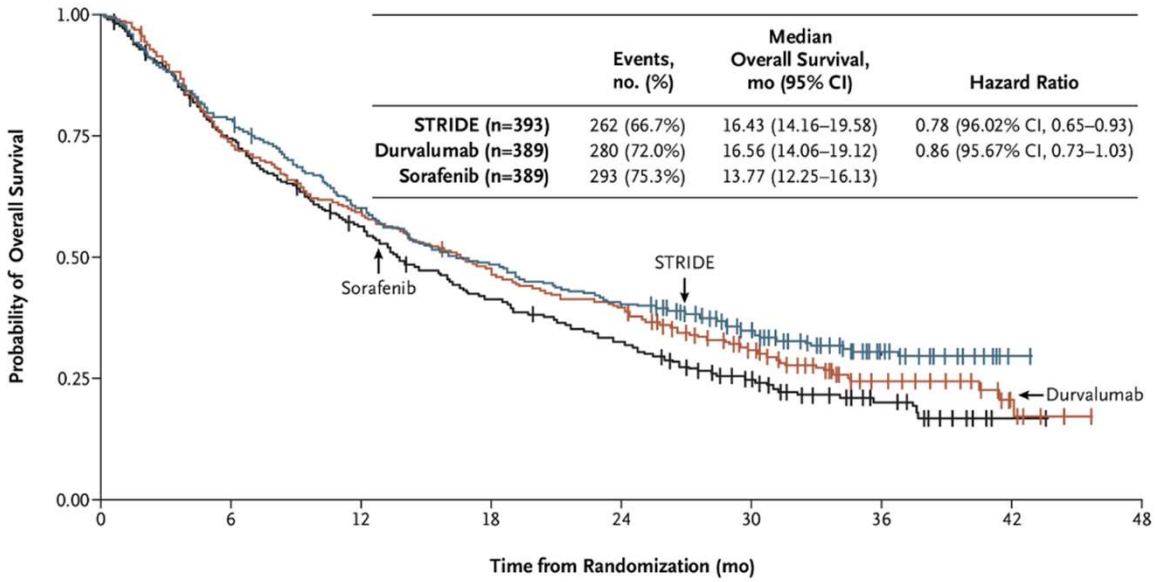
- Mai 2020 : accord FDA
- Novembre 2020 : Accord EMA
- **20/06/20222 : Remboursement** d'atezolizumab + bevacizumab dans l'indication "carcinome hépatocellulaire avancé ou non résécable, n'ayant pas reçu de traitement systémique antérieur, avec une fonction hépatique préservée (Child-Pugh A), un ECOG 0-1, et non éligibles aux traitements locorégionaux ou en échec à l'un de ces traitements".

Immuno / CHC

HIMALAYA



- **STRIDE** = TREMELIMUMAB (300 mg, 1 dose) + DURVALUMAB (1500mg/4 weeks)
- **DURVALUMAB**=1500 mg/4 weeks
- **SORAFENIB =** 400 mg twice daily



	Events, no. (%)	Median Overall Survival, mo (95% CI)	Hazard Ratio
STRIDE (n=393)	262 (66.7%)	16.43 (14.16–19.58)	0.78 (96.02% CI, 0.65–0.93)
Durvalumab (n=389)	280 (72.0%)	16.56 (14.06–19.12)	0.86 (95.67% CI, 0.73–1.03)
Sorafenib (n=389)	293 (75.3%)	13.77 (12.25–16.13)	

No. at Risk									
STRIDE	393	308	235	190	158	98	32	1	0
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

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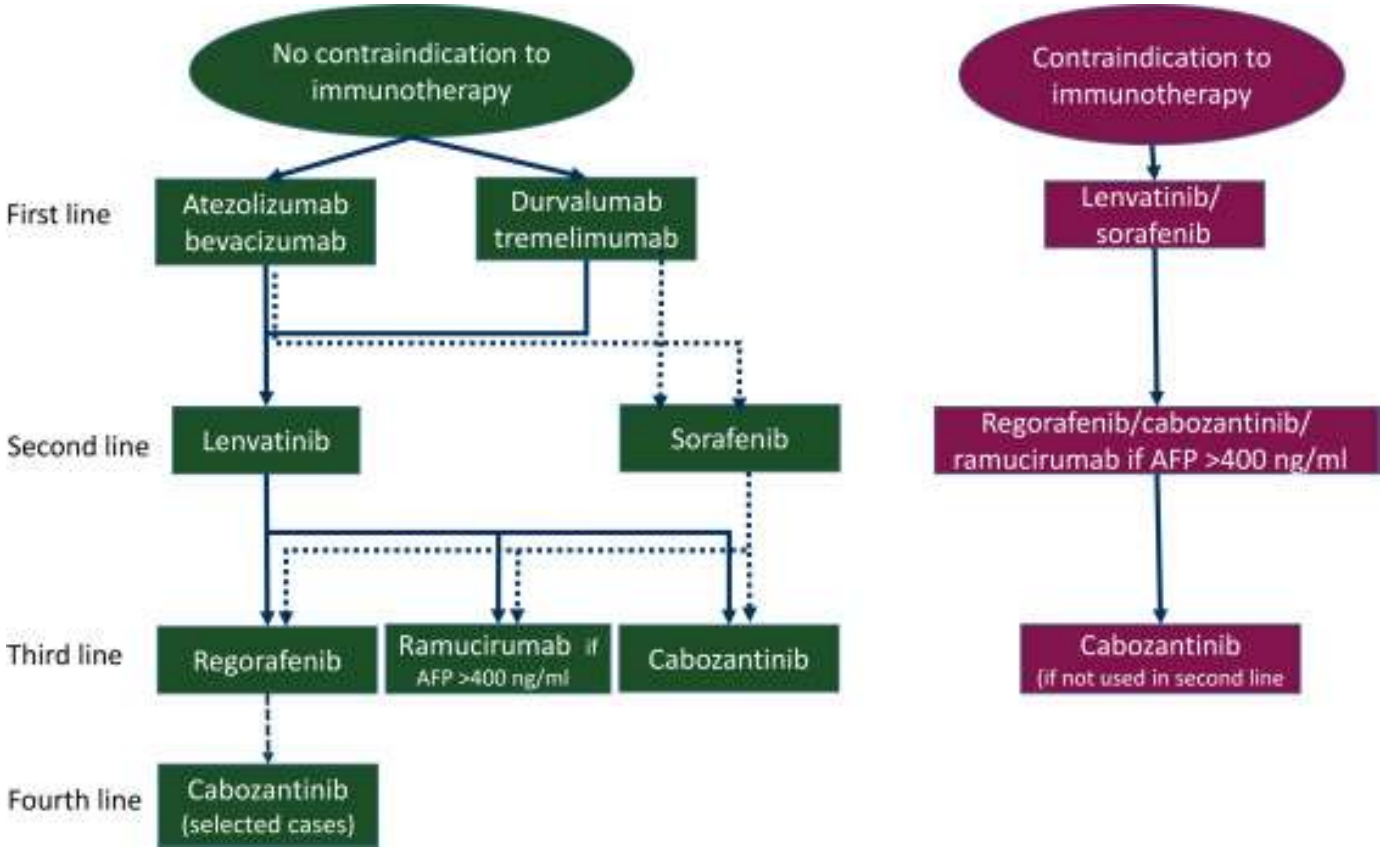
Ghassan K. Abou-Alfa, et al, NEJM Evid 2022;1(8)DOI: 10.1056/EVIDoa2100070

DURVA-TREME CHC

- Oct. 2021 : accord FDA
- Juin 2023 : Accord EMA CHMP
- **Mai 2023 : Accès précoce** dans « le traitement de première ligne des patients adultes atteints d'un carcinome hépatocellulaire (CHC) avancé ou non résécable uniquement chez les patients avec une fonction hépatique préservée (Child-Pugh A), un ECOG 0-1, et non éligibles aux traitements locorégionaux ou en échec à l'un de ces traitements ».
- **PUT-RD en cours.**

Expert opinion and recommendations derived from the 24th ESMO/World Congress on Gastrointestinal Cancer

Guidelines CHC



Ducreux M. et al, ESMO Open 2023 Vol 8(3)

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3 - Tumeurs MSI (hors colorectal)

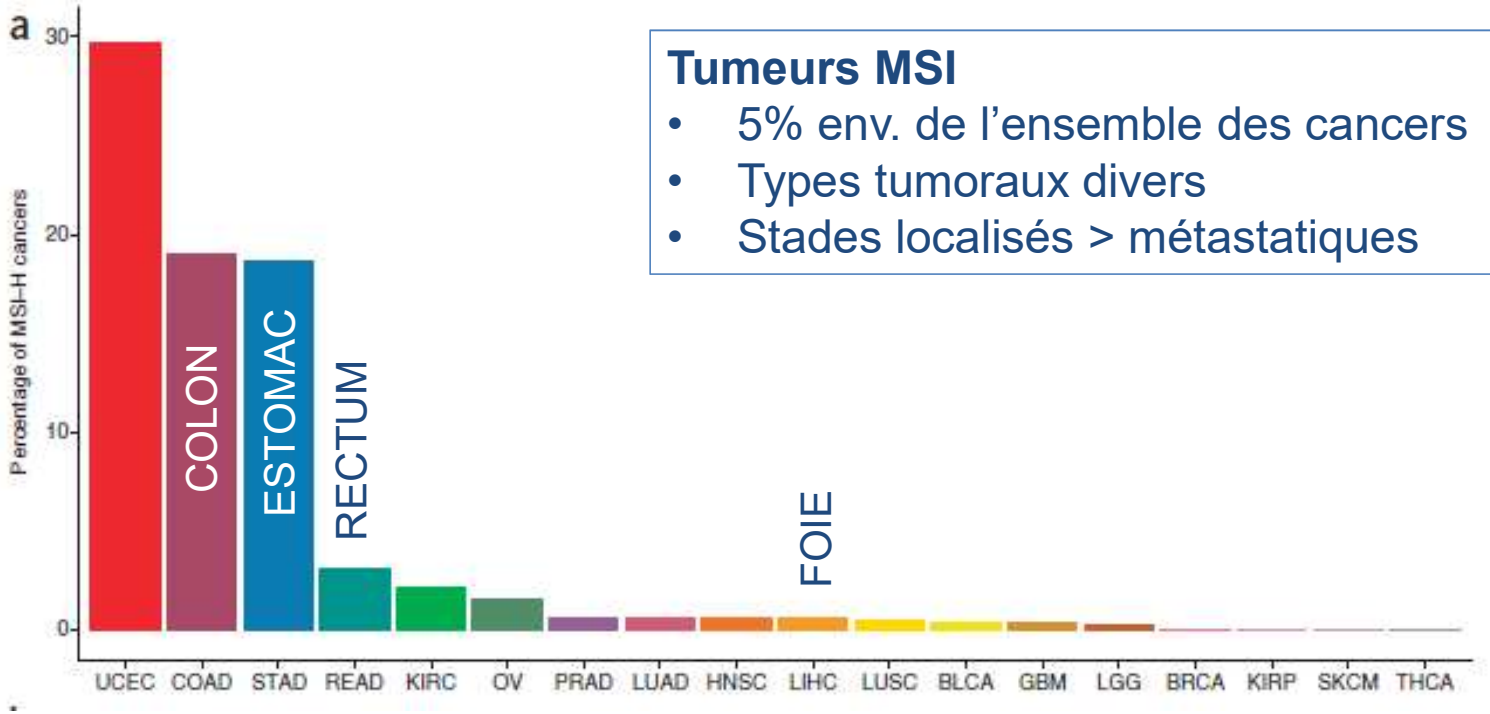
HEPATO-GASTRO & ONCOLOGIE DIGESTIVE
MINI-REVUE

Tumeurs digestives MSI

Immunotherapy in non-colorectal MSI tumors

Christelle de la Fouchardière

Institut Paoli-Calmettes, Département d'Oncologie Médicale, 232 boulevard de Sainte-Marguerite, 13009 Marseille



Tumeurs MSI

- 5% env. de l'ensemble des cancers
- Types tumoraux divers
- Stades localisés > métastatiques

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R.J. Hause, et al Nat Med, 22 (2016), pp. 1342-1350

Tumeurs digestives MSI

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

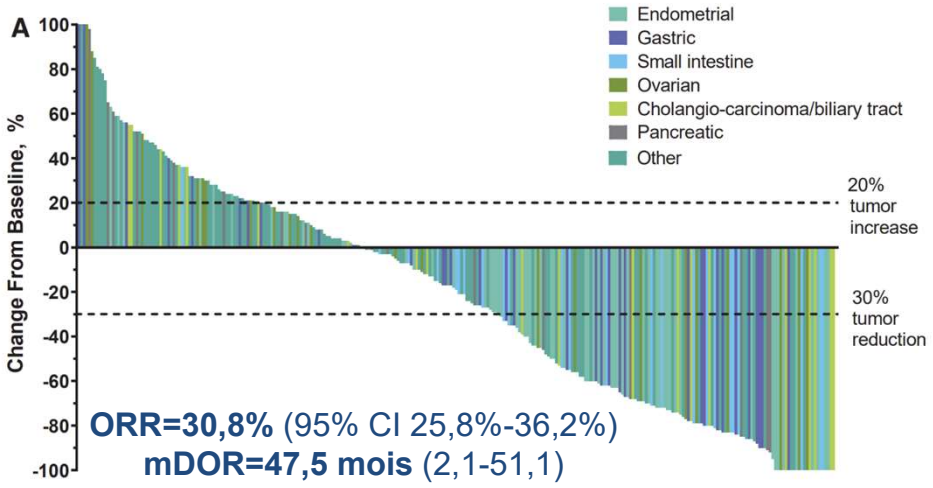
ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study

M. Maio[1*], P. A. Ascierto[2], L. Manzyuk[3], D. Motola-Kuba[4], N. Penel[5], P. A. Cassier[6], G. M. Bariani[7], A. De Jesus Acosta[8], T. Doi[9], F. Longo[10], W. H. Miller, Jr[11,12], D.-Y. Oh[13,14,15], M. Gottfried[16], L. Xu[17], F. Jin[17], K. Norwood[17] & A. Marabelle[18]

- **N= 351 patients pré-traités** (31% ≥ 3 lignes préalables)
- 27 types tumoraux différents
  - ✓ endomètre (n = 79 ; 22,5 %)
  - ✓ estomac (n = 51 ; 14,5 %)
  - ✓ intestin grêle (n = 26 ; 7,4 %).



- Accord EMA en L2
- Pas de remboursement en France

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Table 3. Summary of efficacy outcomes by tumor types with the highest number of enrolled patients

	Endometrial *n* = 68	Gastric *n* = 42	Small intestine *n* = 25	Ovarian *n* = 24	Cholangiocarcinoma/ biliary tract *n* = 22	*Pancreatic n* = 22
ORR, % (95% CI)	48.5 (36.2-61.0)	31.0 (17.6-47.1)	48.0 (27.8-68.7)	33.3 (15.6-55.3)	40.9 (20.7-63.6)	18.2 (5.2-40.3)
Best objective response, *n* (%)						
CR	10 (14.7)	4 (9.5)	4 (16.0)	3 (12.5)	3 (13.6)	1 (4.5)
PR	23 (33.8)	9 (21.4)	8 (32.0)	5 (20.8)	6 (27.3)	3 (13.6)
SD	13 (19.1)	7 (16.7)	7 (28.0)	2 (8.3)	3 (13.6)	3 (13.6)
PD	19 (27.9)	15 (35.7)	5 (20.0)	12 (50.0)	8 (36.4)	8 (36.4)
Not evaluable	1 (1.5)	1 (2.4)	—	—	—	—
No assessment	2 (2.9)	6 (14.3)	1 (4.0)	2 (8.3)	2 (9.1)	7 (31.8)
DOR, median (range), months	NR (2.9 to 47.1+)	NR (6.3 to 51.1+)	NR (2.1+ to 41.8+)	NR (4.2 to 43.5+)	30.6 (6.2 to 40.5+)	NR (8.1 to 24.3+)
Median PFS, months (95% CI)	13.1 (4.9-34.4)	3.2 (2.1-12.9)	23.4 (4.3-NR)	2.2 (2.0-6.2)	4.2 (2.1-24.9)	2.1 (1.9-3.4)
PFS rate ≥3 years[3], %	33.9	28.5	49.1	29.2	12.7	NR
Median OS, months (95% CI)	NR (32.4-NR)	11.0 (5.8-31.5)	NR (16.2-NR)	33.6 (11.0-NR)	19.4 (6.5-NR)	3.7 (2.1-9.8)
OS rate ≥3 years[3], %	62.1	34.5	58.7	42.6	30.3	22.7

Tumeurs digestives MSI

TABLEAU 1 • Études de phase I/II pan-tumeurs évaluant un ICI dans les cancers MSI/dMMR non colorectaux.

	Action	N pts	N pts avec lignes antérieures ≥ 3 (%)	TRO (%)	DMR (mois)	Réf.
Pembrolizumab	Anti-PD-1	351	31	30,8	47,5	[8]
Dostarlimab	Anti-PD-1	81	30	43	Nd	[13]
Nivolumab	Anti-PD-1	42	55	36	Nd	[11]
Tislelizumab	Anti-PD-1	80	nd	46,7	Nd	[12]

DMR = durée médiane de réponse ; TRO = taux de réponse objective. N = nombre ; Nd = non déterminé.

Cancers gastriques MSI

MADRID 2023 ESMO congress

A Phase II study of Nivolumab plus low dose Ipilimumab as 1st line therapy in patients with advanced gastric or esophago-gastric junction MSI-H tumor: First results of the NO LIMIT study (WJOG13320G/CA209-7W7)

K. Muro[1], H. Kawakami[2], S. Kadowaki[1], A. Makiyama[3], M. Tsuda[4], K. Hirata[5], N. Sugimoto[6], N. Machida[7], H. Hara[8], H. Hirano[9], T. Esaki[10], Y. Komatsu[11], S. Hironaka[12]

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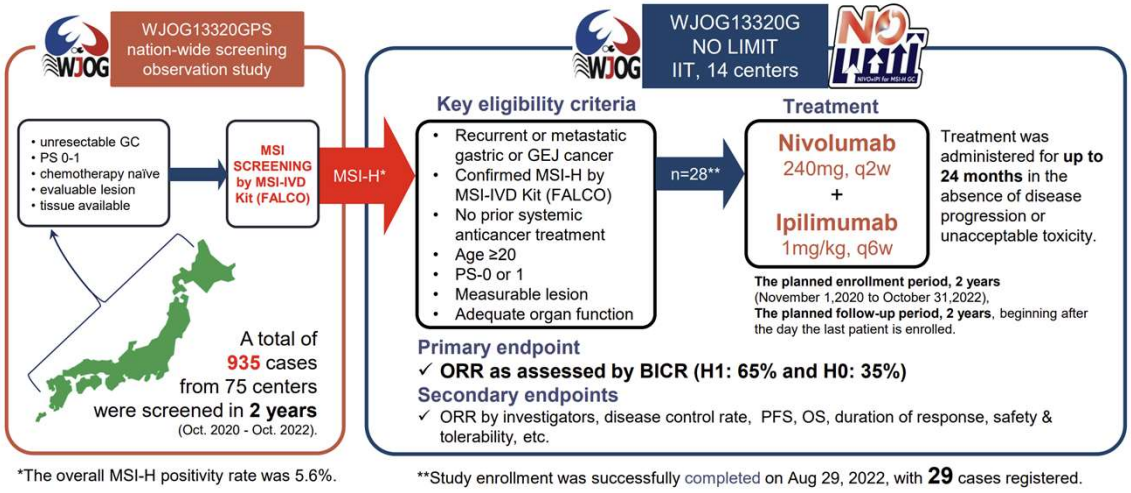

*The overall MSI-H positivity rate was 5.6%.

Study enrollment was successfully completed on Aug 29, 2022, with **29 cases registered.

Responses	n=29
Best ORR per BICR, n(%)	
CR	3 (10.3%)
PR	15 (51.7%)
SD	5 (17.2%)
PD	4 (13.8%)
NE	2 (6.9%)
Confirmed ORR per BICR, % (95% CI)	**62.1 (42.3-79.3)**
Confirmed ORR per Investigator, % (95% CI)	69.0 (49.2-84.7)
DCR per BICR, % (95% CI)	79.3 (60.3-92.0)
Median DOR per BICR, months (95% CI)	NR (12.6-NR)

Checkmate 649

MSI-H

	NIVO + IPI (n = 11)	Chemo (n = 10)
Median OS, mo	NR	10.0
(95% CI)	(2.7-NR)	(2.0-28.2)
Unstratified HR (95% CI)	0.28 (0.08-0.92)	
ORR,* %	70	57
(95% CI)	(35-93)	(18-90)

À suivre …

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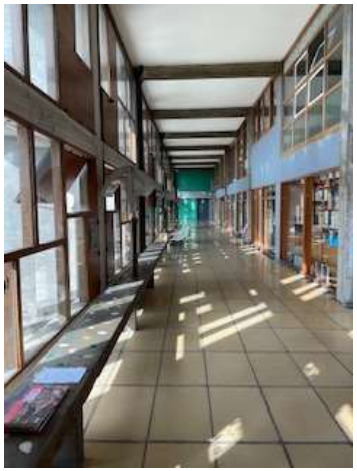
Conclusion

- **Un grand nombre d'indication** d'immunothérapie en oncologie digestive
  - Principalement anti PD1-PD-L1
  - Principalement en combinaison avec chimio
- **Beaucoup d'études en cours**
  - Autres inhibiteurs de checkpoint immunitaires (ICI)
  - Autres indications, autres lignes
  - Autres combinaisons …

- **Manque études de QOL et médico-économiques**
- **Problème d'accès ICI dans tumeurs digestives MSI non colorectales**
- **Biomarqueurs hors PD-L1**

Je vous remercie



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