Current Status of Immunotherapy in GI cancers

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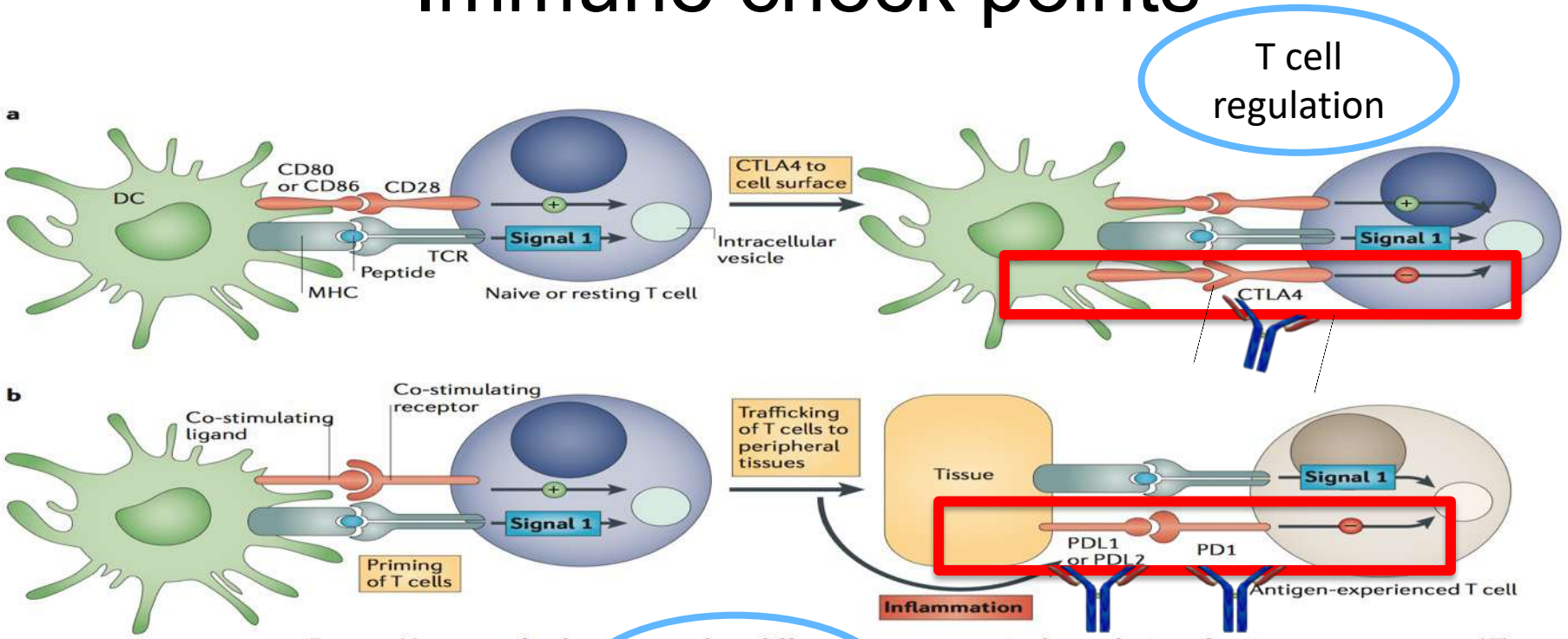
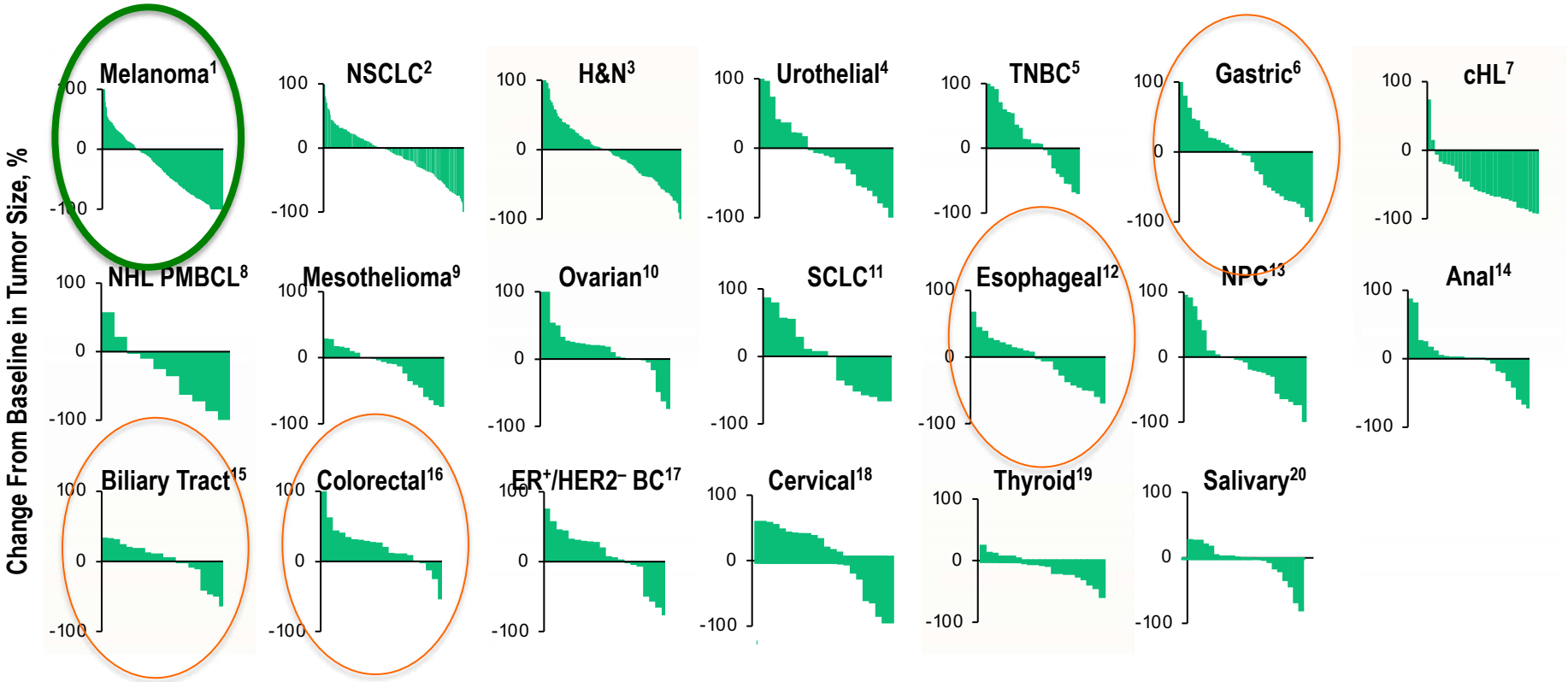
Immune check points



Pardoll DM et al., *Nat Rev Cancer*, 2012

Pan-tumor results with pembrolizumab

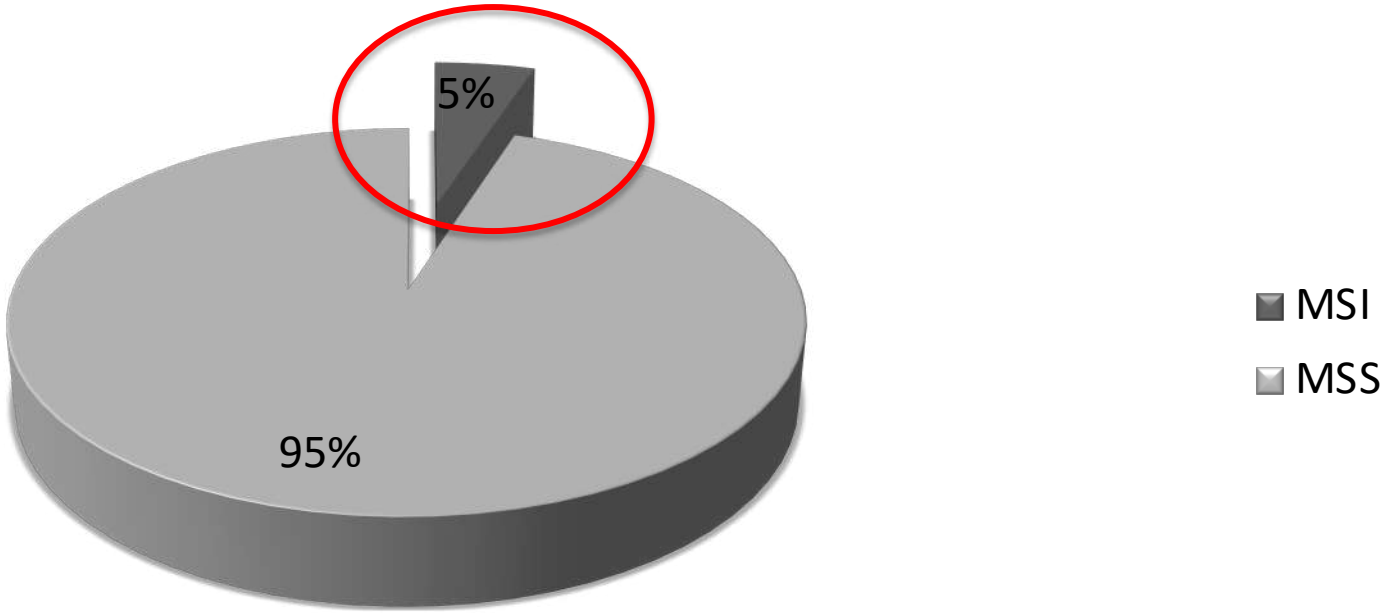


Current status and outlook on immunotherapy in GI cancers

Current status and outlook on immunotherapy in GI cancers

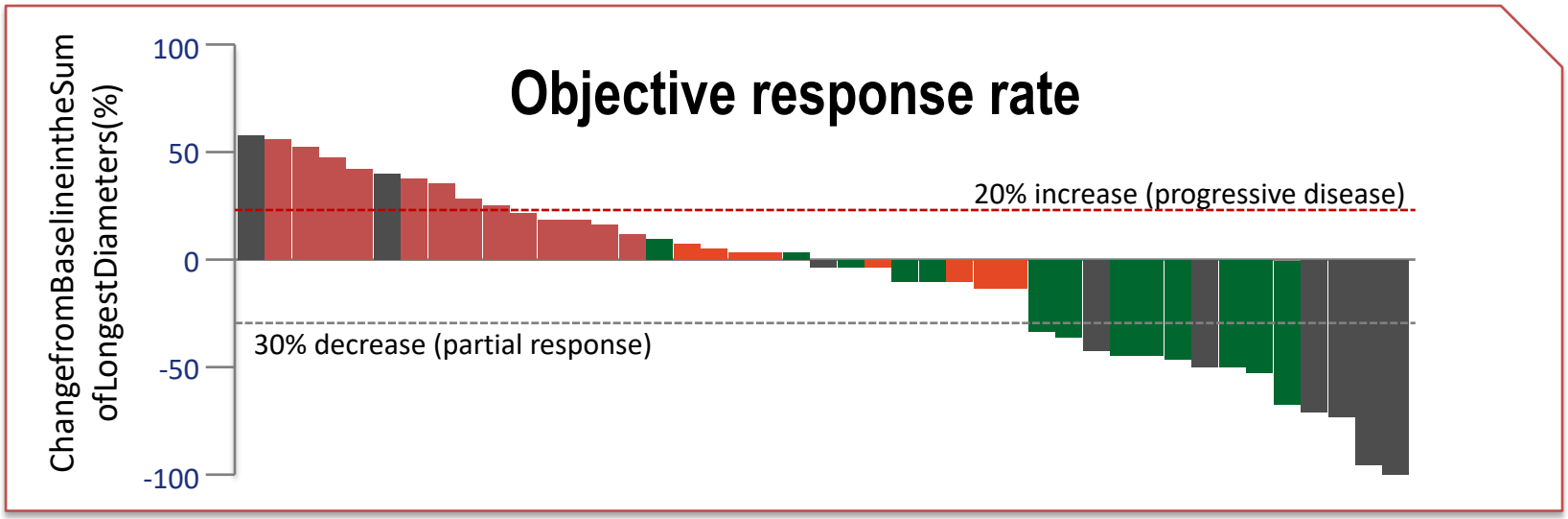
Colorectal cancer

metastatic colorectal cancer



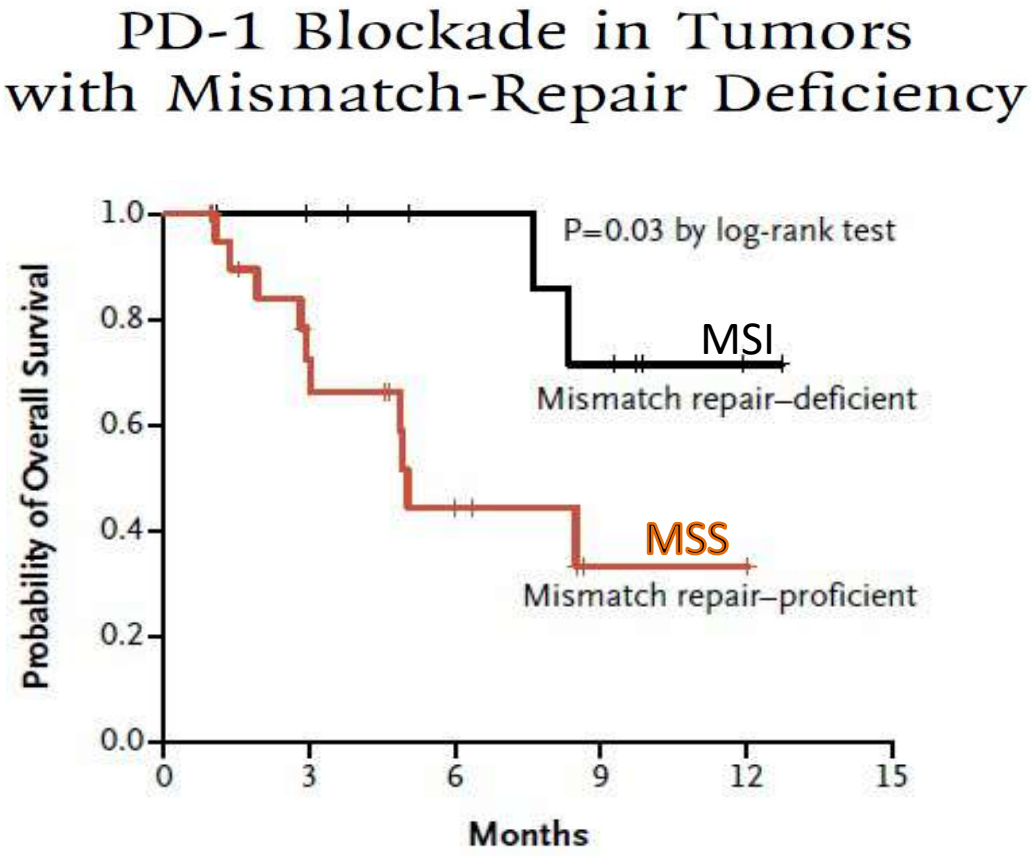
Checkpoint blockers (pembrolizumab: anti-PD1)
Efficacy signal in MSI-H tumors

	MSI-H mCRC	MSS mCRC	MSI-H non CRC
N	13	25	10
ORR	62%	0%	60%



Le DT et al. N Engl J Med 2015

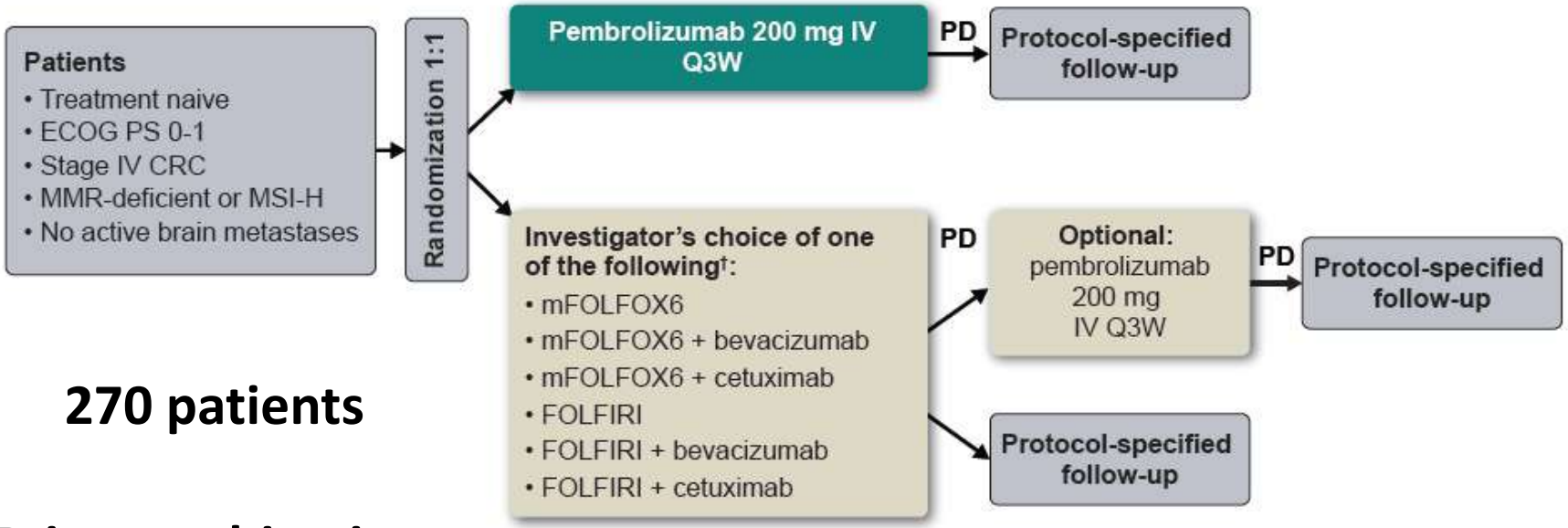
Checkpoint blockers (pembrolizumab: anti-PD1)
Efficacy signal in MSI-H tumors



Le DT et al. N Engl J Med 2015

Keynote 177

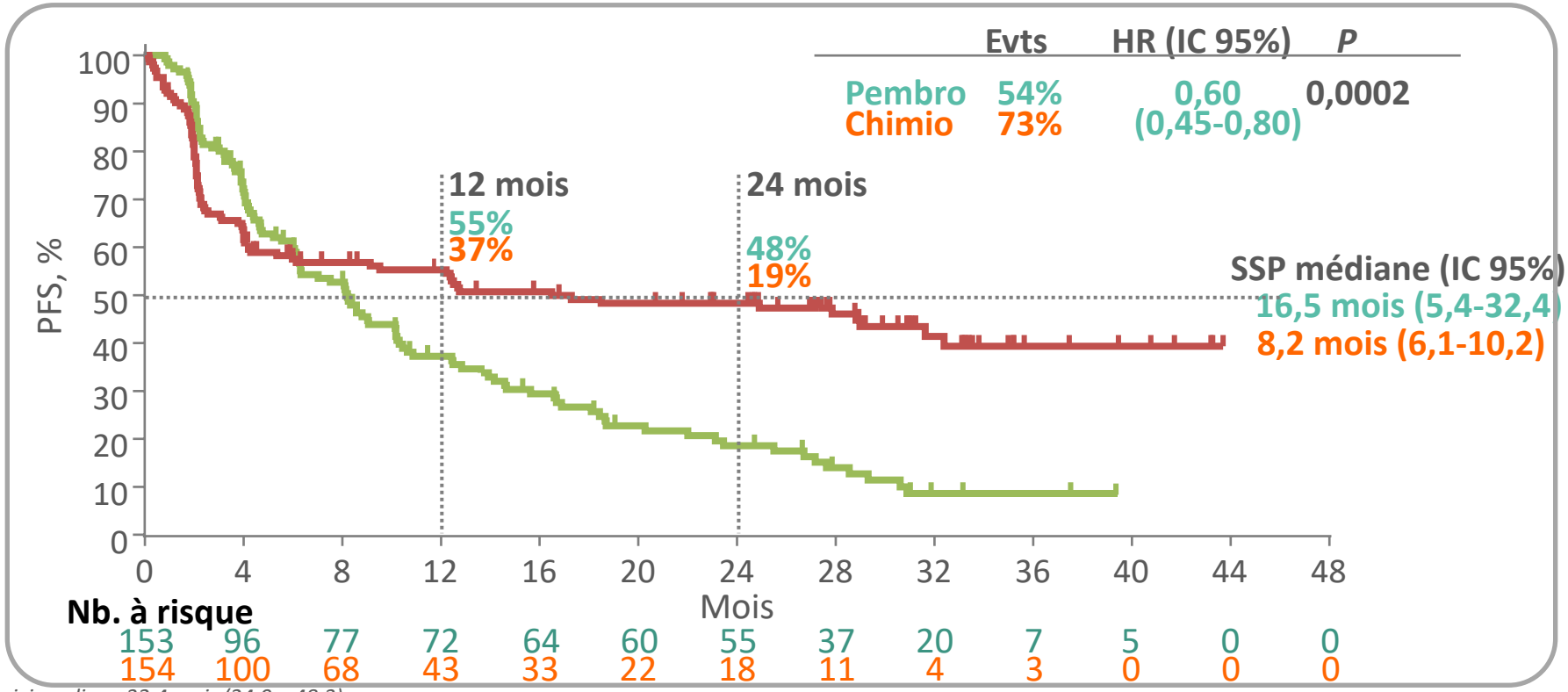
First-line, phase III study of pembrolizumab (anti-PD1) versus investigator-choice chemotherapy for MSI mCRC



270 patients

Primary objective:
PFS

Objectif principal atteint!



Suivi median : 32,4 mois (24,0 – 48,3);

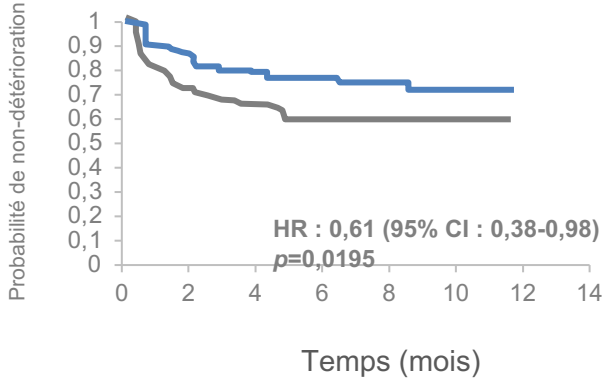
PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR.

Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

T. Andre, et al., ASCO® 2020, Abs #LBA4

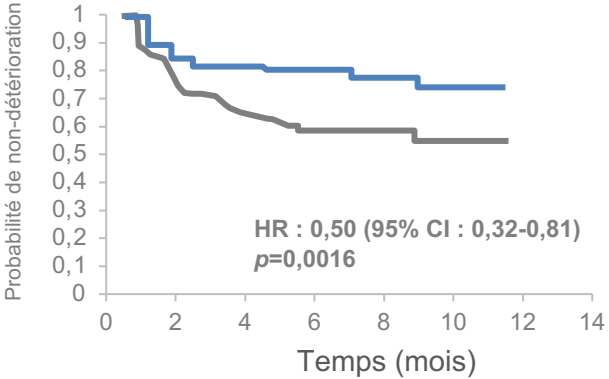
Pembrolizumab *versus* traitement standard en L1 du CCRm MSI : données de Qualité de Vie : ETUDE KEYNOTE-177

- Analyse temps jusqu'à détérioration
- Exemple QLQ-C30 et capacités physiques



	Evts (n)	SSP médiane (95% CI)
Pembro	30	NA (NA-NA)
CTR	39	NA (NA-NA)

	Evts (n)	SSP médiane (95% CI)
Pembro	29	NR (NR-NR)
CTR	45	NR (5,2-NR)



Nb. À risque								
Pembro	141	104	82	71	58	42	0	0
CRT	131	85	57	32	25	10	0	0

Pembro	141	103	84	74	66	43	0	0
CRT	131	83	54	31	23	10	0	0

Profil en faveur du bras Pembro

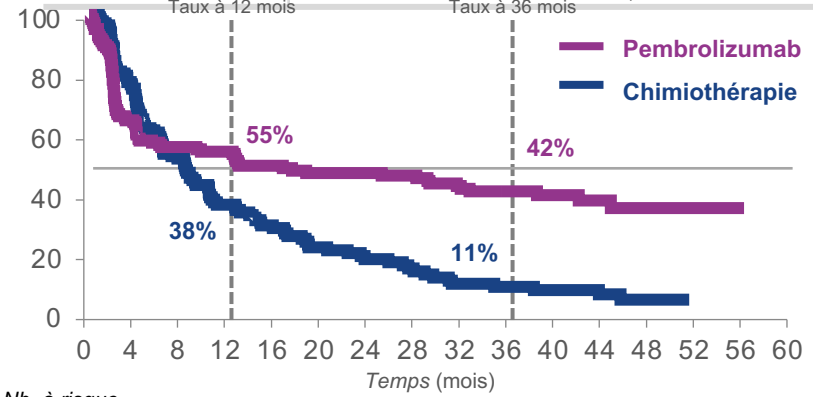
Conclusion

- Différence significative des indicateurs de QdV en faveur du bras Pembro.
- Reflet du bénéfice clinique et profil de tolérance du traitement.

KN177: survie sans progression

Survie sans progression (SSP)

	Pembrolizumab (n=153)	Chimiothérapie (n=154)
Evènements (%)	**56**	**76**
SSP médiane, mois (IC 95%)	**16,5** (5,4 - 38,1)	**8,2** (6,1 - 10,2)
HR (IC 95%)	**0,59** (0,45 - 0,79)	



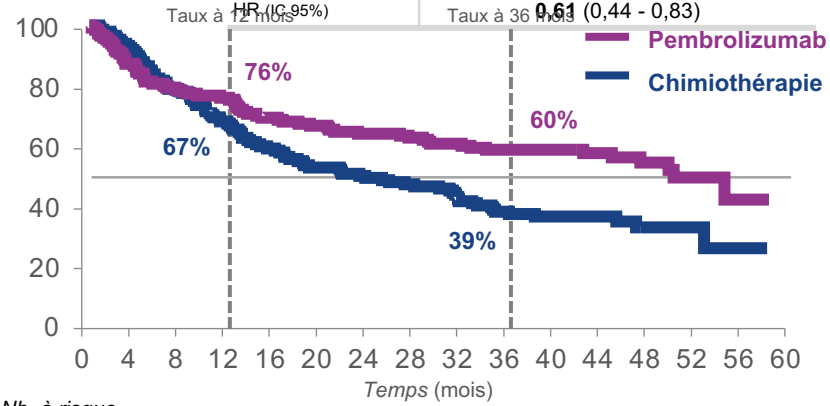
Nb. à risque

153	96	77	72	64	60	59	55	50	42	28	16	7	5	0	0
154	101	69	45	35	25	21	16	12	11	8	5	3	0	0	0

Survie sans progression 2 (SSP2)

Délai entre la randomisation et la progression ou le décès sur la ligne de traitement ultérieure.

	Pembrolizumab (n=153)	Chimiothérapie (n=154)
Evènements (%)	**44**	**62**
SSP2 médiane, mois (IC 95%)	**54,0** (44,4 to NR)	**24,9** (16,6-32,6)
HR (IC 95%)	**0,61** (0,44 - 0,83)	



Nb. à risque

153	131	120	116	107	103	99	97	93	87	67	43	26	15	3	0
154	136	117	100	86	78	73	69	62	53	43	29	11	6	2	0

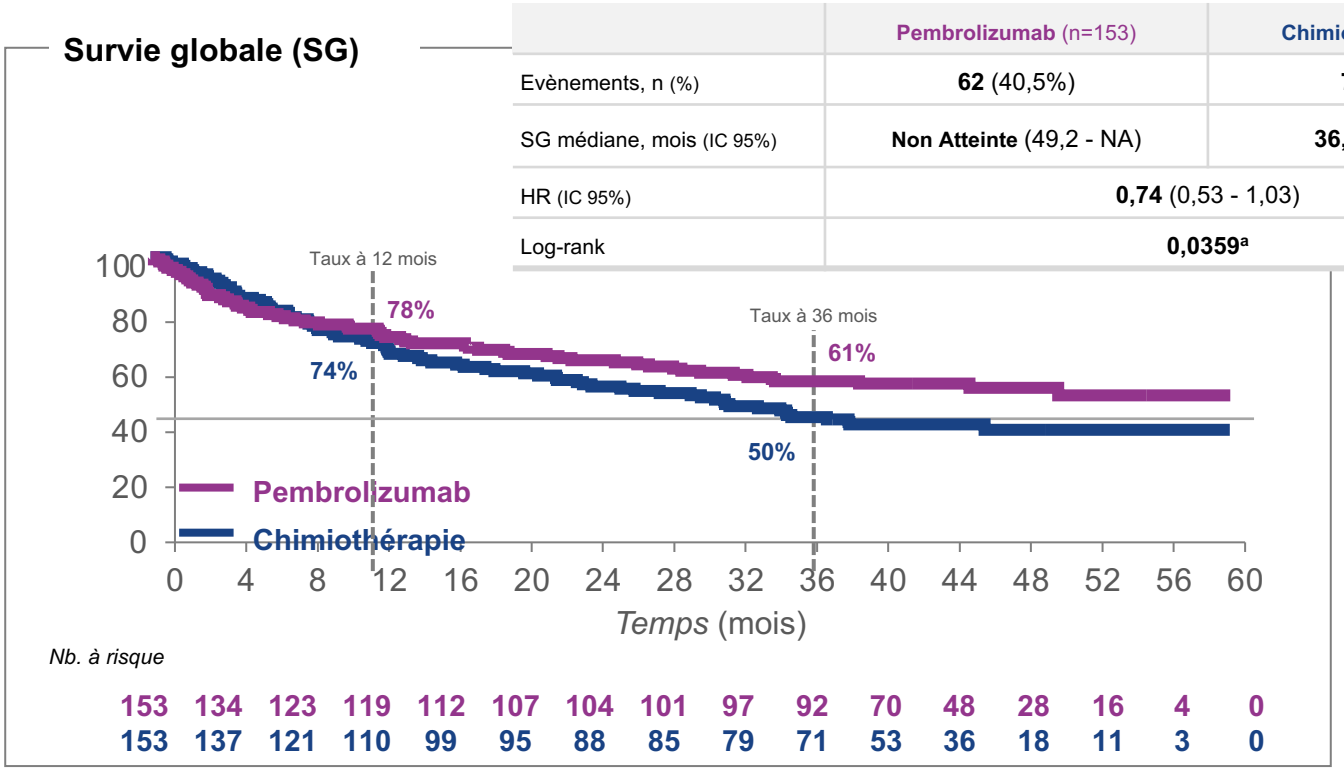
Réponse tumorale

	Pembrolizumab N = 153	Chimiothérapie N = 154
Taux de réponse objective, n (%)	**69 (45,1)[a]**	**51 (33,1)**
Meilleure réponse, n (%)		
Réponse Complète	**20 (13,1)[b]**	**6 (3,9)**
Réponse Partielle	**49 (32,0)[c]**	**45 (29,2)**
Stabilisation	**30 (19,6)**	**65 (42,2)**
Taux de contrôle de la maladie (RC+RP+SM)	**99 (64,7)**	**116 (75,3)**
Progression	**45 (29,4)**	**19 (12,3)**
Non évaluable	**3 (2,0)**	**2 (1,3)**
Non accessible	**6 (3,9)**	**17 (11,0)**
Median duration or response (range), mo	**NA (2,3+ à 53,5+)**	**10,6 (2,8 à 48,3+)**
≥ 24 months response duration, %	**83,5**	**33,6**

aORR 43.8%; bCR rate 11.1%; cPR rate 32.7% at IA2 (data cut-off 19Feb2020).
Data cut-off: 19Feb2021.

Survie Globale: crossover pembro or other ICI = 60%

	Pembrolizumab (n=153)	Chimiothérapie (n=153)
Evènements, n (%)	**62** (40,5%)	**78** (50,6%)
SG médiane, mois (IC 95%)	**Non Atteinte** (49,2 - NA)	**36,7** (27,6 - NA)
HR (IC 95%)	**0,74** (0,53 - 1,03)	
Log-rank	**0,0359**[a]	



[a] *Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38). Data cut-off: 19Feb2021.*

Conclusions

- Le Pembrolizumab augmente la SSP, le taux et la durée de réponse vs la chimio-biothérapie chez les patients atteints d'un CCRm MSI-H
- Le profil de tolérance et le schéma d'administration sont aussi en faveur du Pembrolizumab

  → Effets secondaires de grades ≥3 (22% vs 66%)

  → Amélioration de la QdV
- La PFS 2 et la SG sont en faveur de l'immunothérapie même si la significativité n'est pas atteinte (60% de "cross-over")

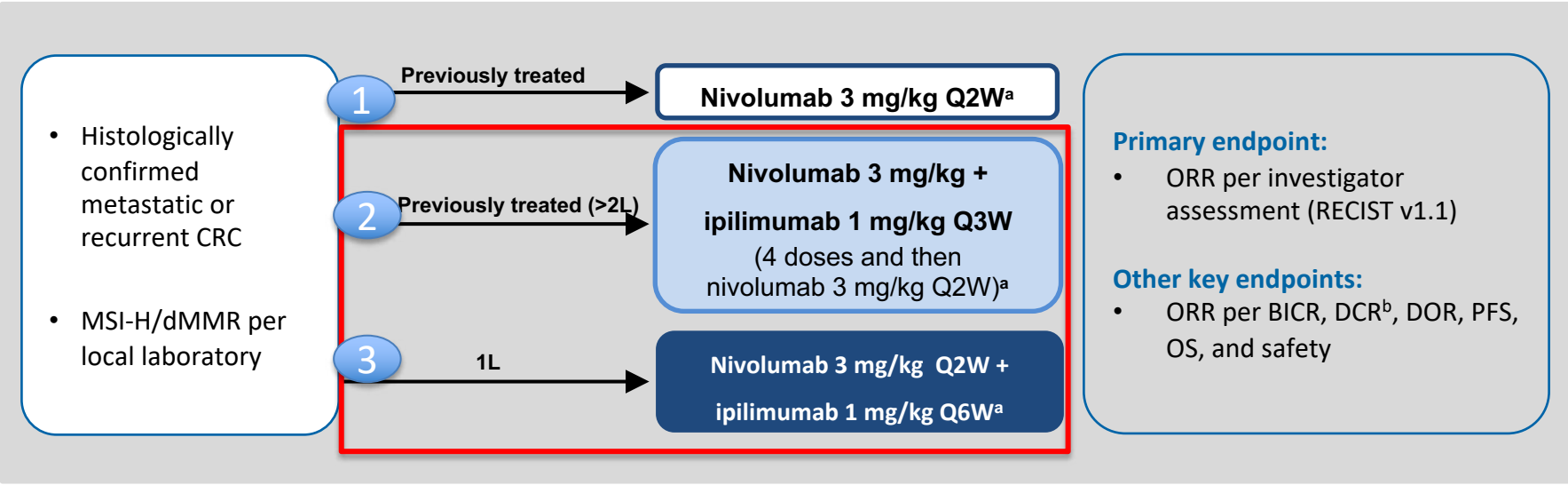
Confirme le Pembrolizumab comme nouveau standard de L1 pour les CCRm MSI-H

Association avec la chimiothérapie en cours pour éviter la perte de chance initiale pour un petit % de patients

Combination of immunotherapy in MSI mCRC ?

CheckMate-142 Study Design

- CheckMate-142 is an ongoing, multi-cohort, nonrandomized phase 2 study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC (NCT02060188)



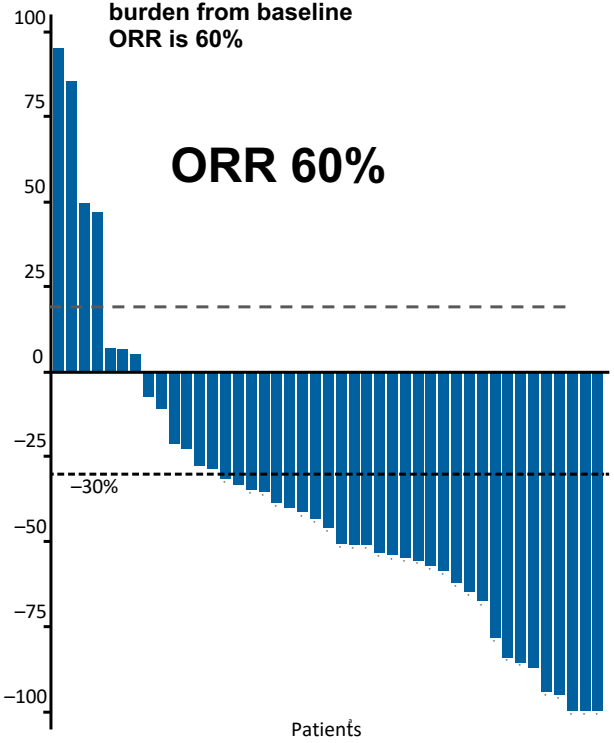
[a]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end; [b]Patients with a CR, PR, or SD for ≥12 weeks divided by the number of treated patients; [c]Time from first dose to data cutoff

BICR = blinded independent central review; CR = complete response; CRC = colorectal cancer; DCR = disease control rate; DOR = duration of response; PFS = progression-free survival; PR = partial response; Q2W = once every 2 weeks; Q3W = once every 3 weeks; Q6W = once every 6 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

Overall Response Rate

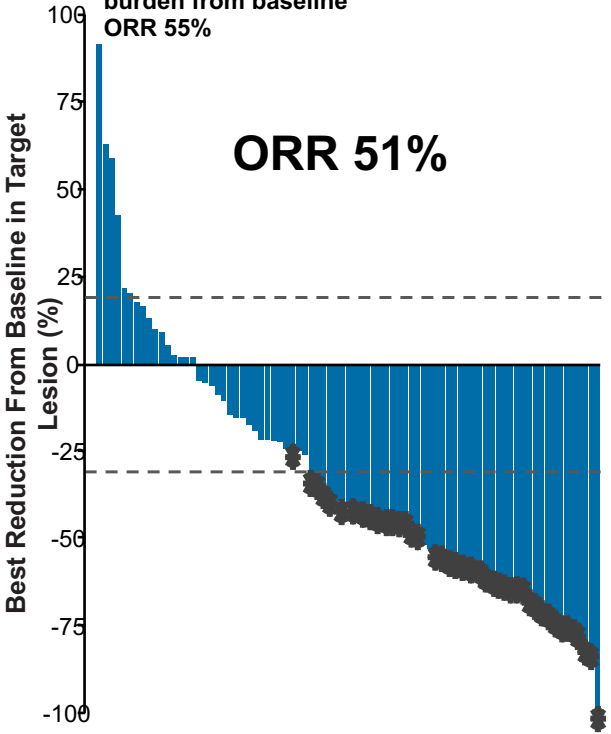
NIVO + IPI L1 (n = 44)

84% of patients had reduction in tumor burden from baseline
ORR is 60%



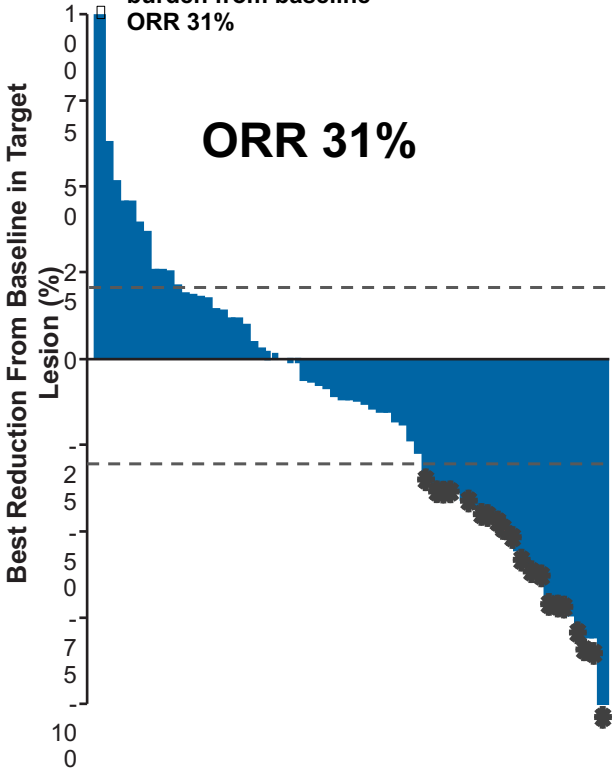
NIVO + IPI >L2 (n = 84)

80% of patients had reduction in tumor burden from baseline
ORR 55%



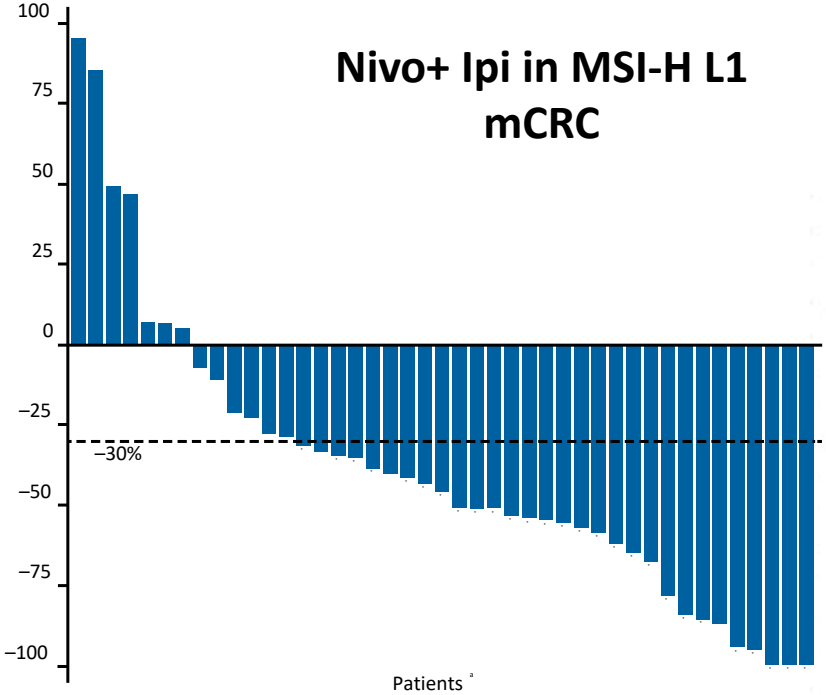
NIVO Monotherapy >L2 [1] (n = 74)

69% of patients had reduction in tumor burden from baseline
ORR 31%



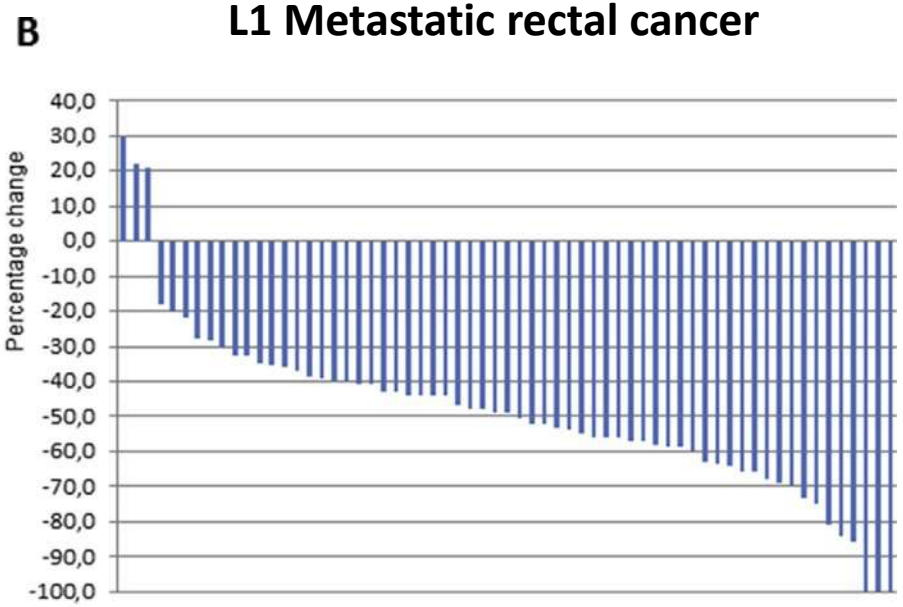
*Confirmed CR or PR per investigator % Change truncated at 100

Are these results incredible?



Nivo+ Ipi in MSI-H L1 mCRC

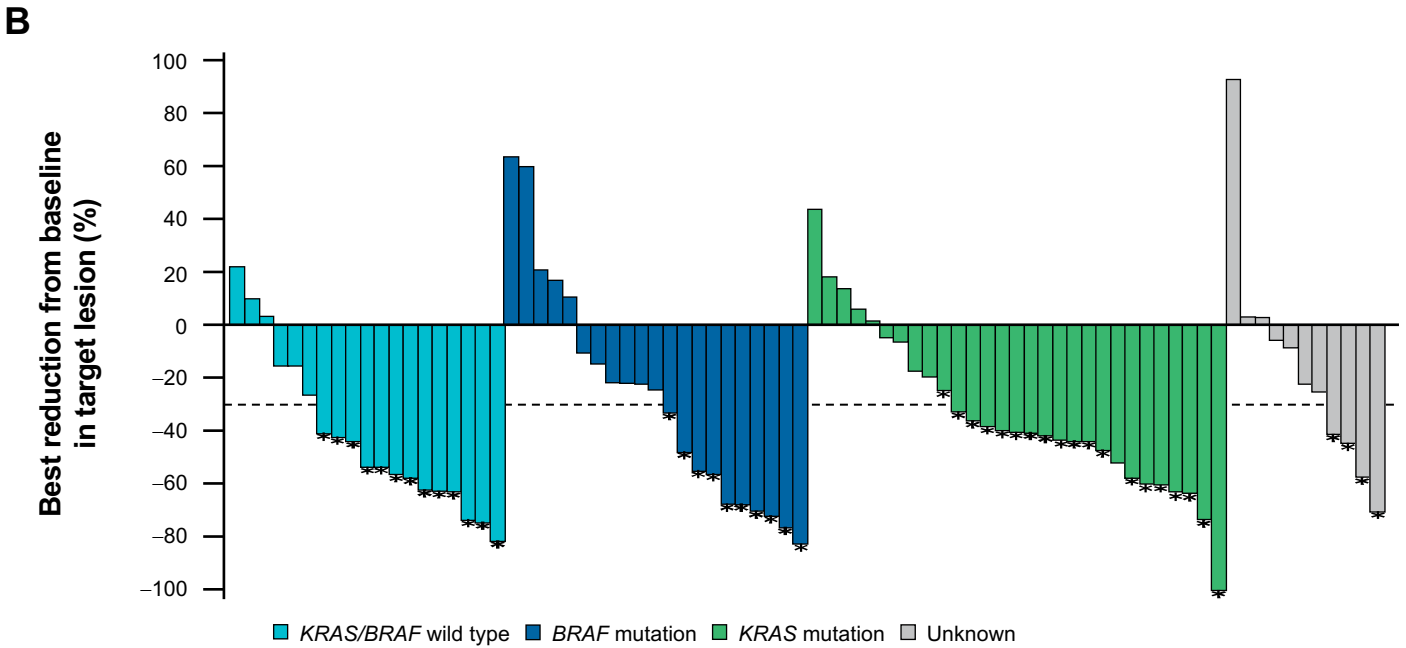
FOLFIRINOX in all comers L1 Metastatic rectal cancer



Bachet et al. EJC 2018

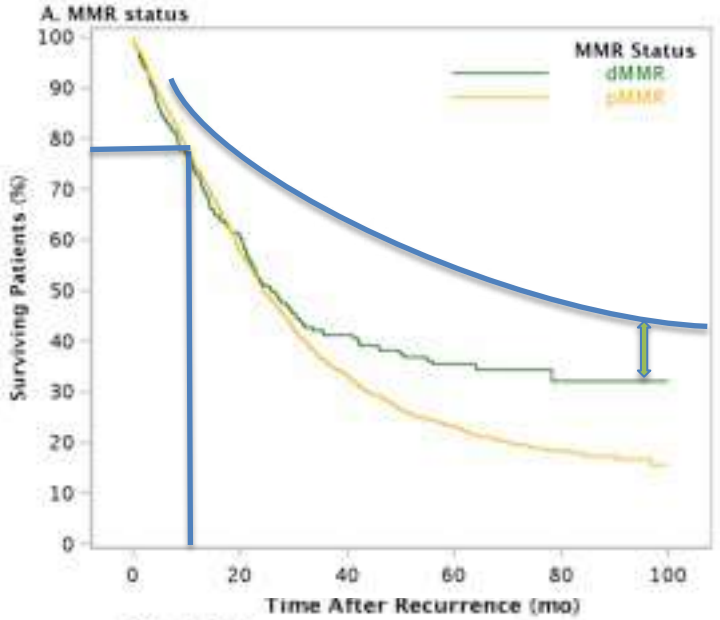
No major differences in RAS mut, BRAF mut and double wild type patients

Figure 2. Association of best reduction in target lesion size (B) BRAF and KRAS mutation status in patients with dMMR/MSI-H mCRC treated with NIVO + IPI



What is MSI-H patients mCRC survival ???

Immunotherapy
May change things
after 1 year

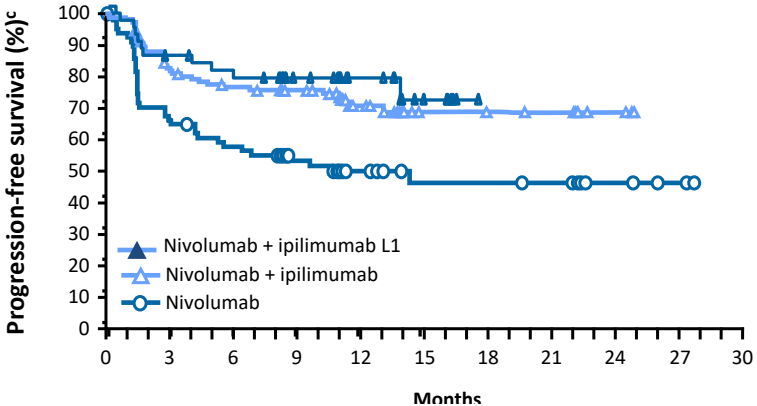


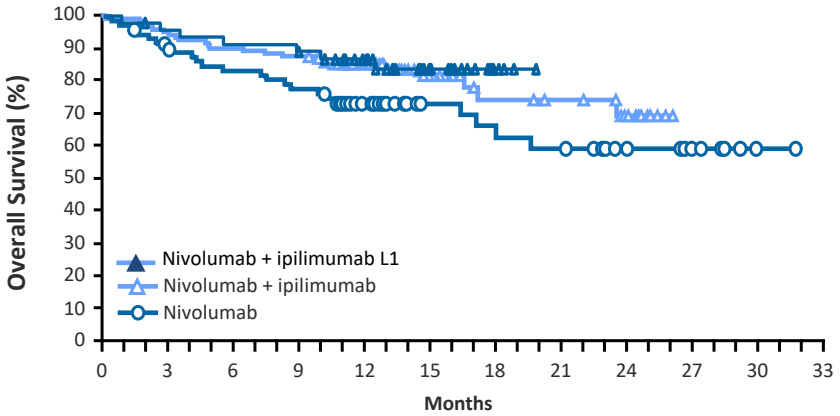
Immunotherapy

Progression-Free and Overall Survival

	Nivo+ Ipi L1	Nivolumab + ipilimumab	Nivolumab[1]
9-mo (95% CI), %	**77** (62.0–87.2)	76 (67.0, 82.7)	54 [41.5, 64.5]
12-mo (95% CI], %	**77** (62.0–87.2)	71 (61.4, 78.7)	50 [38.1, 61.4]

	Nivo+ Ipi L1	Nivolumab + ipilimumab	Nivolumab
9-mo (95% CI), %	**89** (74.9–95.1)	87 (80.0, 92.2)	78 [66.2, 85.7]
12-mo (95% CI), %	**83**(67.6–91.7)	85 (77.0, 90.2)	73 [61.5, 82.1]





- Combination therapy provided improved long-term clinical benefit relative to monotherapy during a similar follow-up period[a,e,f]

Overman M, J Clin Oncol. 2018, André T, ASCO GI 2018, Lenz HJ ESMO 2018

Safety of Nivolumab ± Ipilimumab

	NIVO3 (Q2W) + IPI1 (Q6W) 1L N = 45	NIVO3 (Q2W) Previously treated[1] N = 74	NIVO3 + IPI1 (Q3W) x 4, then NIVO3 (Q2W) Previously treated[2] N = 119
Median follow-up[a] (range), months	13.8 (9–19)	13.4 (10–32)[3]	13.4 (9–25)
Any TRAE, n (%)			
Any grade	35 (78)	52 (70)	87 (73)
Grade 3-4	**7 (16)**	**15 (20)**	**38 (32)**
Any TRAE leading to discontinuation, n (%)			
Any grade	**3 (7)**	**5 (7)**	**15 (13)**
Grade 3-4	1 (2)	4 (5)	12 (10)

- Nivolumab plus low-dose ipilimumab in 1L is well tolerated, with a safety profile that is comparable to nivolumab monotherapy in previously treated patients with MSI-H/dMMR mCRC[b]

[a]Median follow-up, defined as time from first dose to data cutoff
[b]**CheckMate 142 monotherapy and combination therapy cohorts were neither randomized nor designed for a formal comparison**
1. Overman MJ, et al. *Lancet Oncol* 2017;18:1182–1191; 2. Overman MJ, et al. *J Clin Oncol* 2018;8:773–779.

Neoadjuvant immunotherapy in colorectal cancer

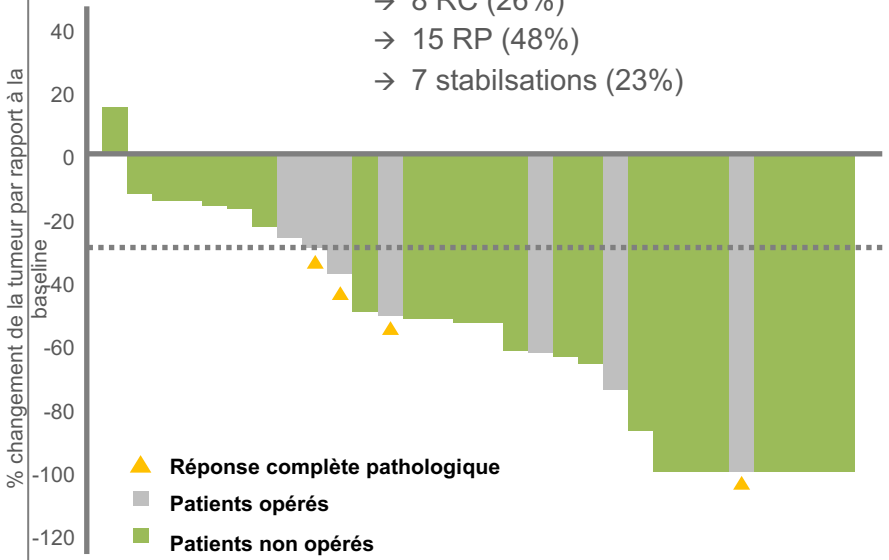
Pembolizumab néoadjuvant dans les cancers MSI

59 pts inclus: résultats préliminaires

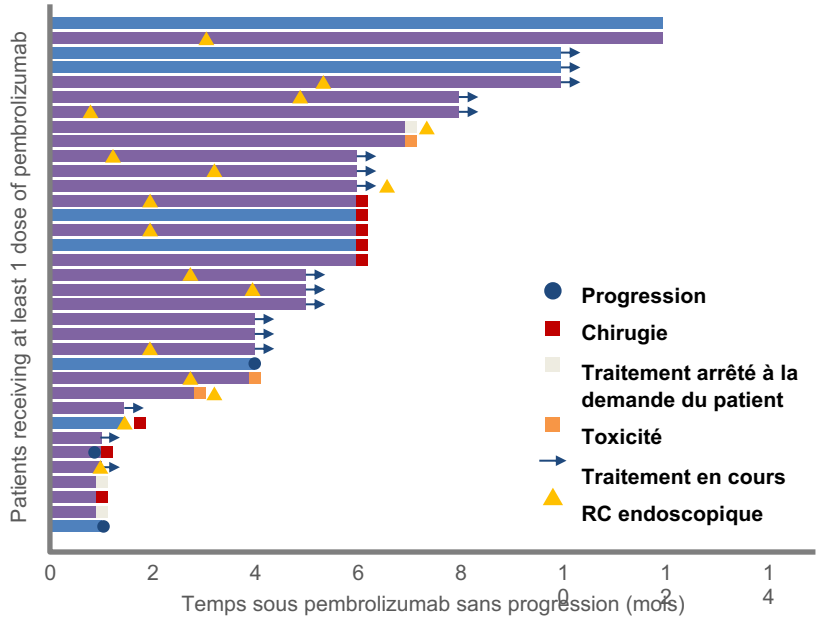
- Patients opérés : 8
  → 4 en pRC (50%) et 3 en near pRC (38%)

Waterfall plot de la meilleure réponse de 31 patients évaluables (RECIST v1.1)

→ 8 RC (26%)
→ 15 RP (48%)
→ 7 stabilsations (23%)



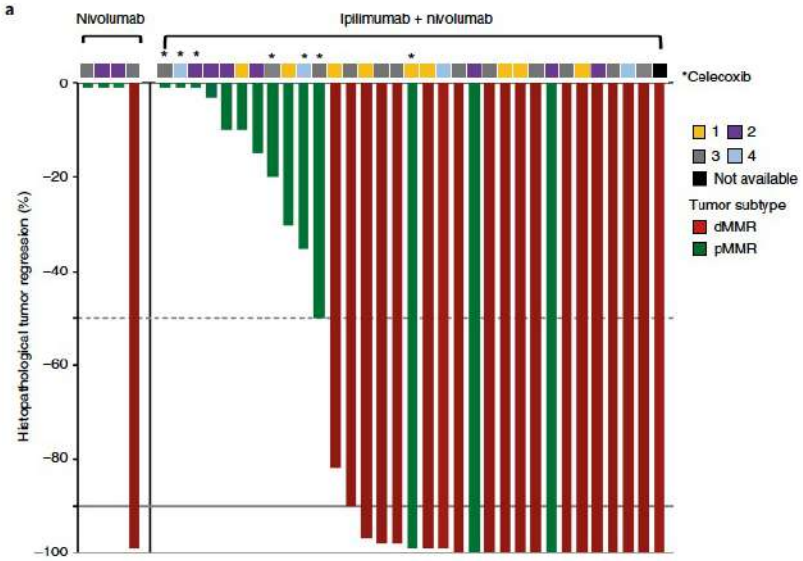
Swimmer plot (non luminal en orange et luminal en bleu)

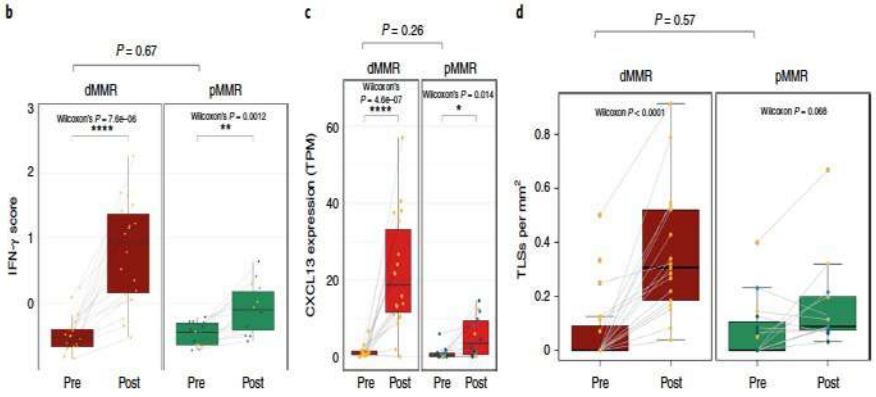


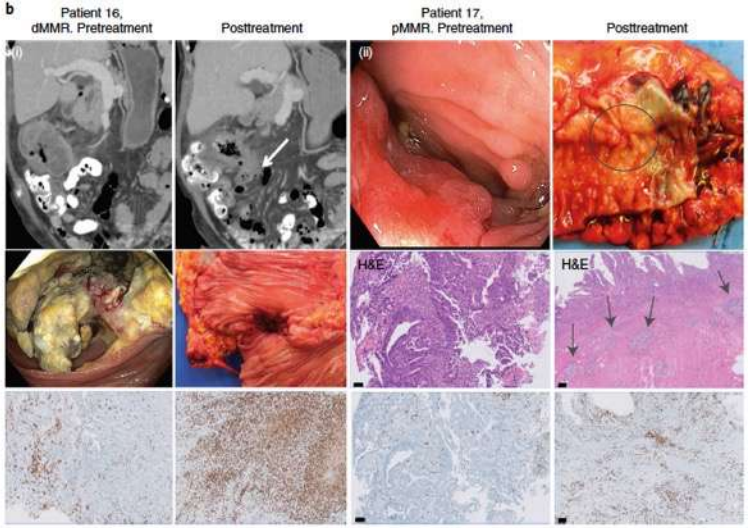
ARTICLES
https://doi.org/10.1038/s41591-020-0805-8
nature medicine
Check for updates

Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

Myriam Chalabi[1,2,3], Lorenzo F. Fanchi[2,4,17], Krijn K. Dijkstra[2,4,17], José G. Van den Berg[5,17],







Etude AVANA

Etude de Phase II

Patients avec cancer du rectum localement avancé (N=101)

- Risque élevé cT3
- cT4
- CN+

CTRT + Avelumab 10 mg/kg toutes les 2 sem, pour 6 cycles

→ **Chirurgie**

TME
8-10 sem après CTRT

→ **CT adjuvante**

Selon la réponse pathologique
(Xelox or Capécitabine pour 6 cycles)

Critère primaire :

- pRC

Critères secondaires :

- Taux de résection R0
- Downstaging tumoral
- Rechute locale
- Taux de préservation sphinctérienne
- SSP
- SG
- Profil de tolérance
- Évaluation de biomarqueurs exploratoires prédictifs et/ou pronostiques

Statistiques :

- P0 : taux de pRC 15%
- Erreur-α (one-side) : 0,05
- Erreur-β : 0,20

- 101 patients nécessaires pour détecter une augmentation absolue de 10 % du taux de pRC
- Le traitement expérimental est retenu pour des études ultérieures si une pRC est observée chez au moins 22 patients.

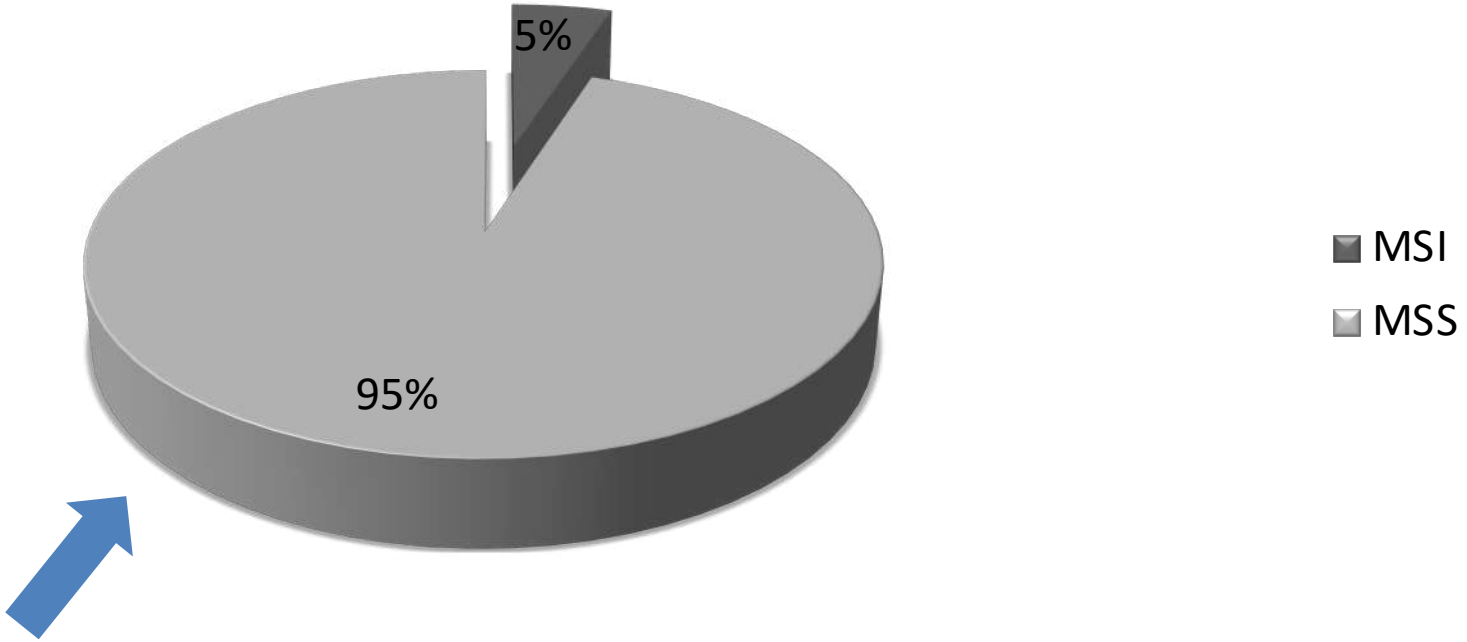
Réponse pathologique complète : 23/100 (23%)
Réponse pathologique majeure : 60/100 (60%)

L. Salvatore et al., ASCO2021, Abs #3511

MSI mCRC

- **Pembrolizumab is the new first line standard treatment for MSI mCRC**
- **How to optimise IO use in patients resistant (≈20%) will have to be studied**
- **Neoadjuvant immuno seems promising, need for randomized studies, can we avoid surgery?**
- **New studies are coming testing IO combos and combination with chemotherapy**

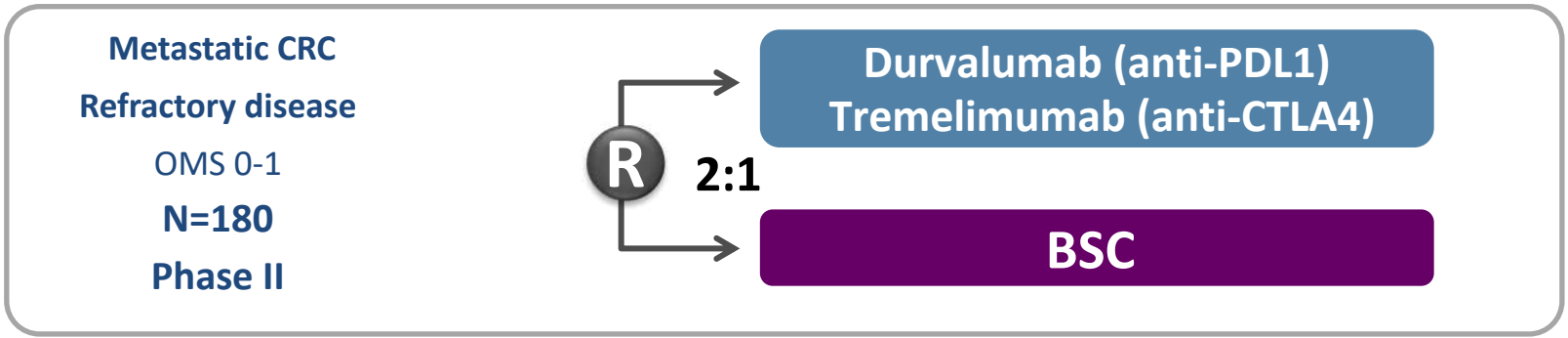
Metastatic Colorectal Cancer



Tumor mutational burden (TMB): predictive marker for immunotherapy ?

TMB: evaluation of the number of somatic mutations into tumour

→ High TMB = more neoantigens that may respond to immunotherapy ?

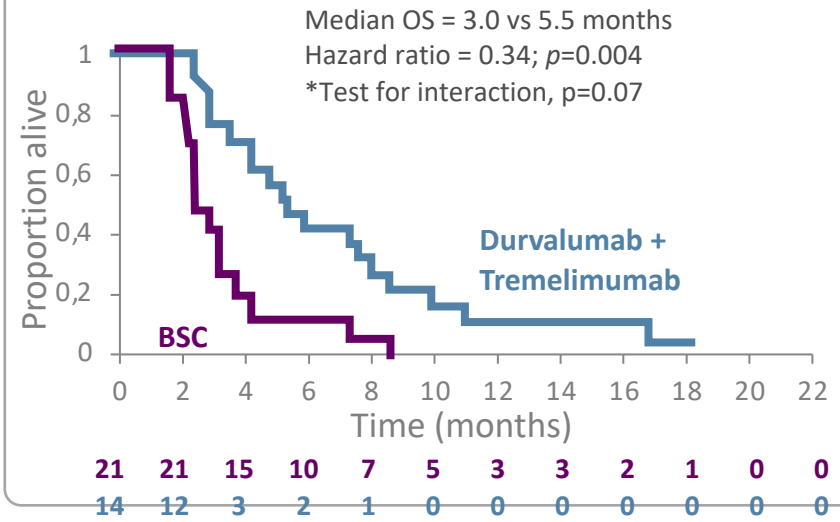


Primary objective : Overall survival according to the TMB

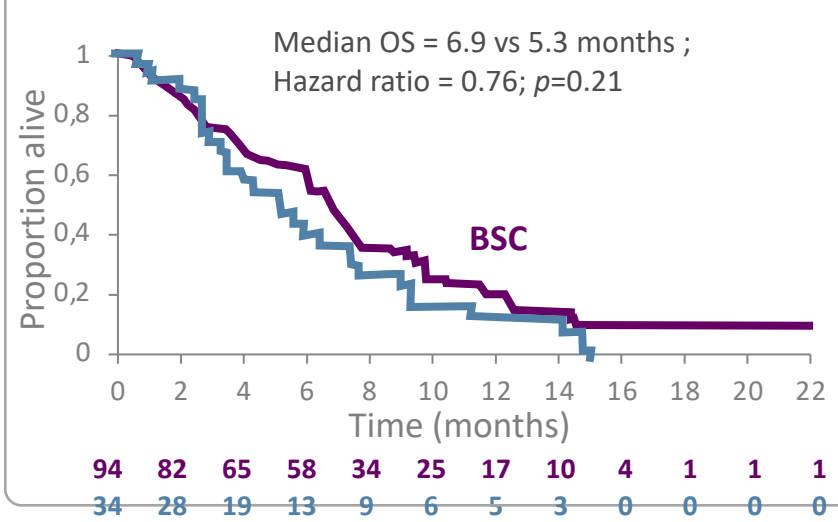
E Xueyu et al., ASCO® 2019, Abs #3512

Tumor mutational burden (TMB): predictive marker for immunotherapy ?

OS for pts with High TMB



OS for pts with low TMB

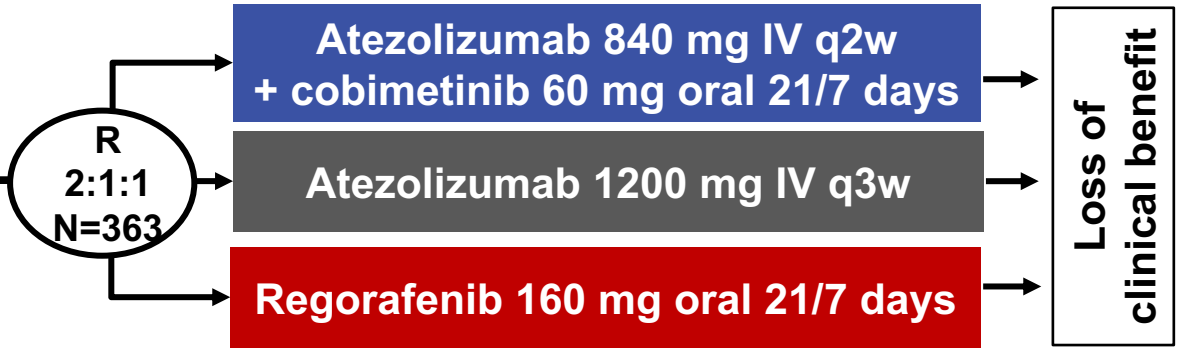


High TMB: TMB>28/Mb; Low TMB: TMB<28/MB

E Xueyu et al., ASCO® 2019, Abs #3512

IMblaze370: randomised, Phase III, multicentre, open-label study in mCRC

- Unresectable locally advanced or metastatic CRC
- Received ≥ 2 prior regimens of cytotoxic chemotherapy for metastatic disease
- ECOG PS 0-1
- MSI-H capped at 5%



Stratification

- Extended *RAS* mutation status (≥ 50% patients in each arm)
- Time since diagnosis of first metastasis (< 18 months vs ≥ 18 months)

Primary endpoint

- OS[a]
  - Atezo + cobi vs rego
  - Atezo vs rego
- Data cutoff date: March 9, 2018

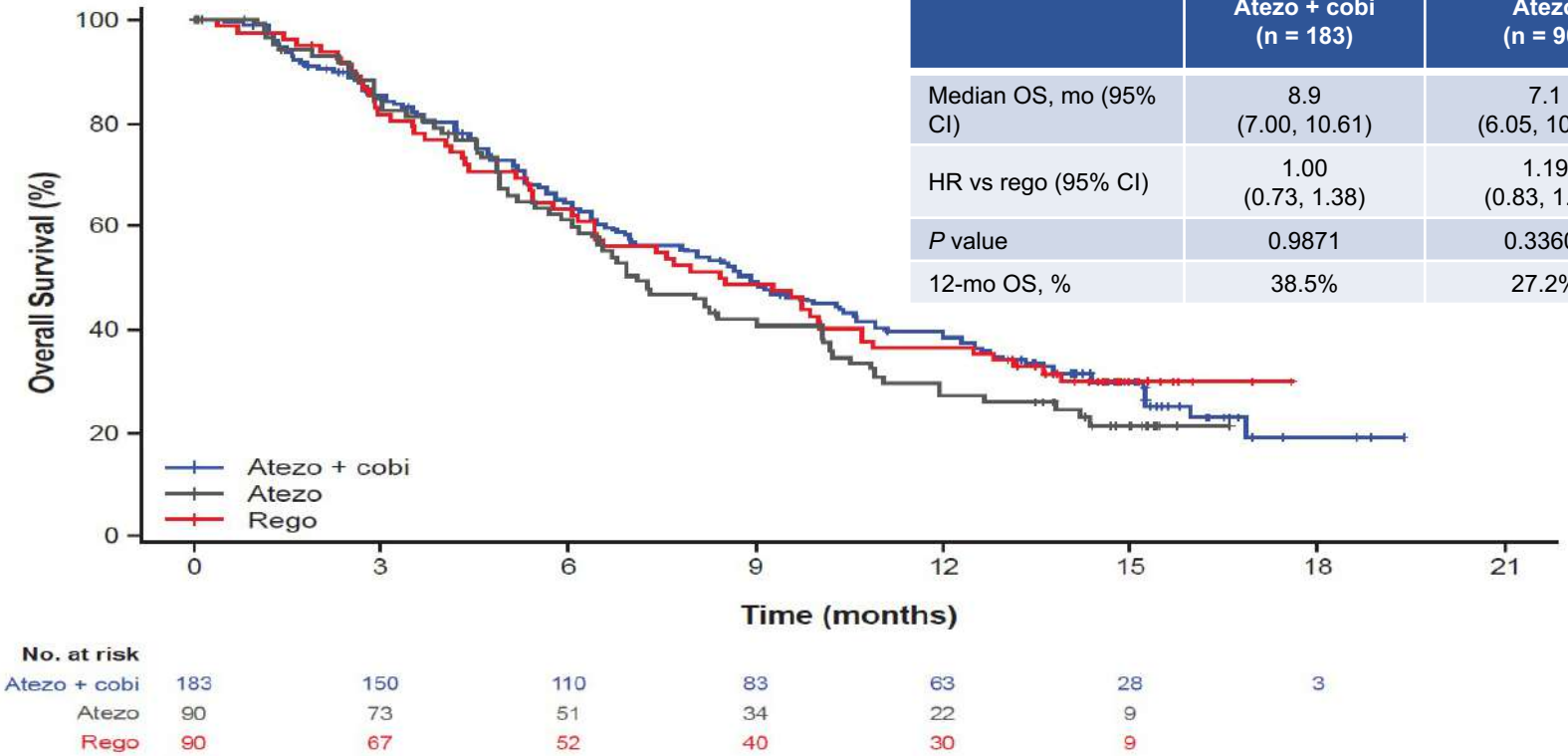
INV-assessed key secondary endpoints

- PFS
- ORR
- DOR

Atezo, atezolizumab; cobi, cobimetinib; INV, investigator; rego, regorafenib.

[a] Two-sided type I error rate of 0.05 was controlled by hierarchical testing (testing atezo vs rego only if atezo + cobi vs rego was positive). NCT02788279

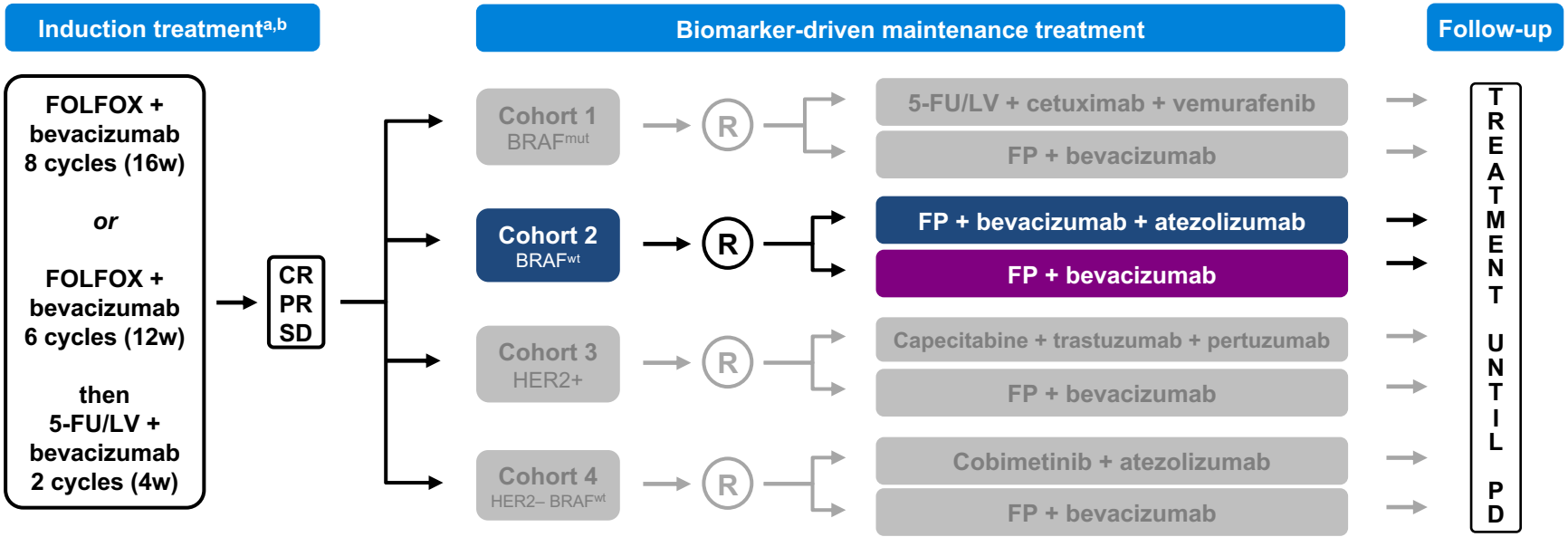
Overall survival



	Atezo + cobi (n = 183)	Atezo (n = 90)	Rego (n = 90)
Median OS, mo (95% CI)	8.9 (7.00, 10.61)	7.1 (6.05, 10.05)	8.5 (6.41, 10.71)
HR vs rego (95% CI)	1.00 (0.73, 1.38)	1.19 (0.83, 1.71)	N/A
P value	0.9871	0.3360[a]	N/A
12-mo OS, %	38.5%	27.2%	36.6%

N/A, not applicable. HRs are from stratified log-rank tests.
Data cutoff: March 9, 2018. [a] For descriptive purposes only.

MODUL: Cohort 2 (1L BRAF^{wt})



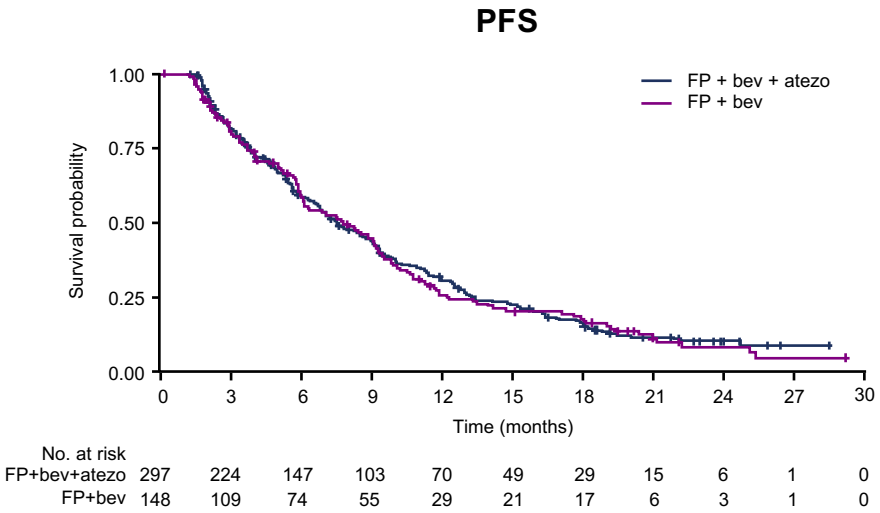
Primary objective: Progression-free survival (PFS; RECIST v1.1) measured from randomization in each maintenance treatment cohort

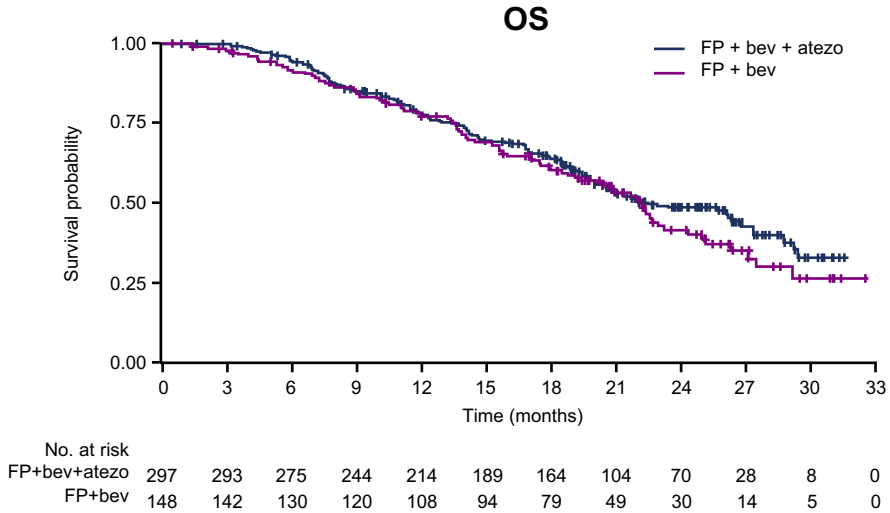
Secondary objectives: Overall survival (OS); overall response rate (ORR); disease control rate (DCR); time to treatment response (TTR); duration of response (DoR); change in ECOG performance status; safety

[a]Key eligibility criteria: histologically confirmed mCRC; measurable, unresectable disease (RECIST 1.1); no prior chemotherapy for mCRC; age ≥18 years; ECOG PS ≤2
[b]Patients with disease progression following Induction treatment can receive further treatment at the discretion of their physician

Updated analysis: 1L BRAF^{wt}

Median follow-up 18.7 months





	FP + bev + atezo	FP + bev
Median PFS, months	7.20	7.39
Stratified HR (95% CI)	0.96 (0.77–1.20)	
p=0.727		

	FP + bev + atezo	FP + bev
Median OS, months	22.05	21.91
Stratified HR (95% CI)	0.86 (0.66–1.13)	
p=0.283		

Median duration of induction treatment phase: 4.1 months; for OS, 31% of patients had an event
One MSI patient in the FP + bev + atezo arm had a complete response during the maintenance treatment phase

Immunotherapy for MSS mCRC

How to better select patients ? Biomarkers ?

- ⇒ **PolE or PolD mutations**
- ⇒ **Immunoscore**
- ⇒ **Specific molecular subgroup (CMS4?)**
- ⇒ **Tumor mutational burden**
- ⇒ **…**

Can we make a cold tumor hot?

- ⇒ **Combine with MEK inhibitors ?**
- ⇒ **Combine with anti-angiogenic agents ?**
- ⇒ **Combine with chemotherapy that induces immunogenic cell deaths ?**
- ⇒ **Combine with radiation therapy to induce abscopal effect ?**
- ⇒ **…**

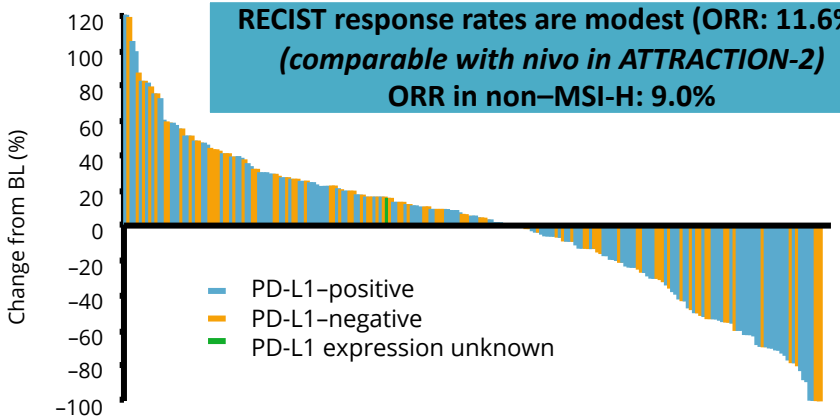
Immunotherapy in GI cancers

Gastric cancer

KEYNOTE-059 (phase II)

Pembrolizumab in chemorefractory mGC

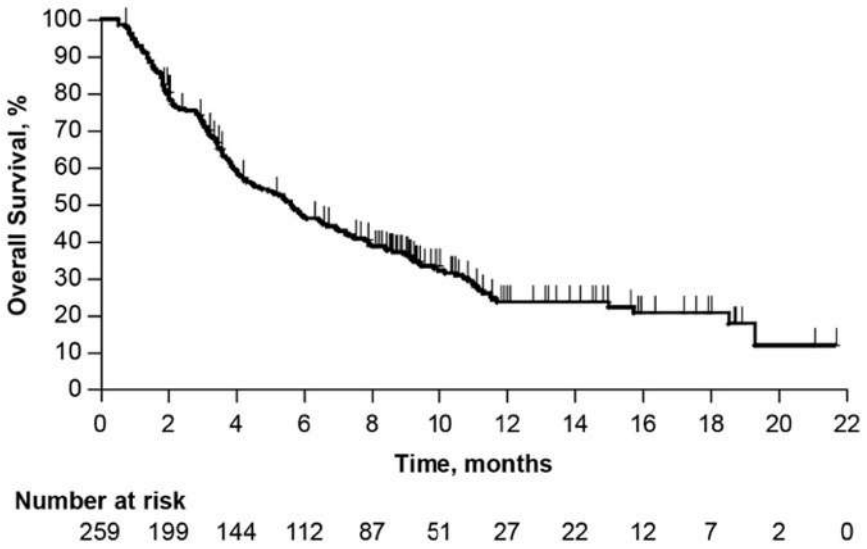
RECIST response rates are modest (ORR: 11.6%)
(comparable with nivo in ATTRACTION-2)
ORR in non–MSI-H: 9.0%



	PD-L1 status	
	Positive (n=148)	**Negative** (n=109)
ORR %(range)	15.5 (10.1–22.4)	6.4 (2.6–12.8)

BL, baseline; MSI-H, microsatellite instability-high

Median response duration were 16.3 vs 6.9 months in patients with PD-L1-positive vs PDL1-negative tumors

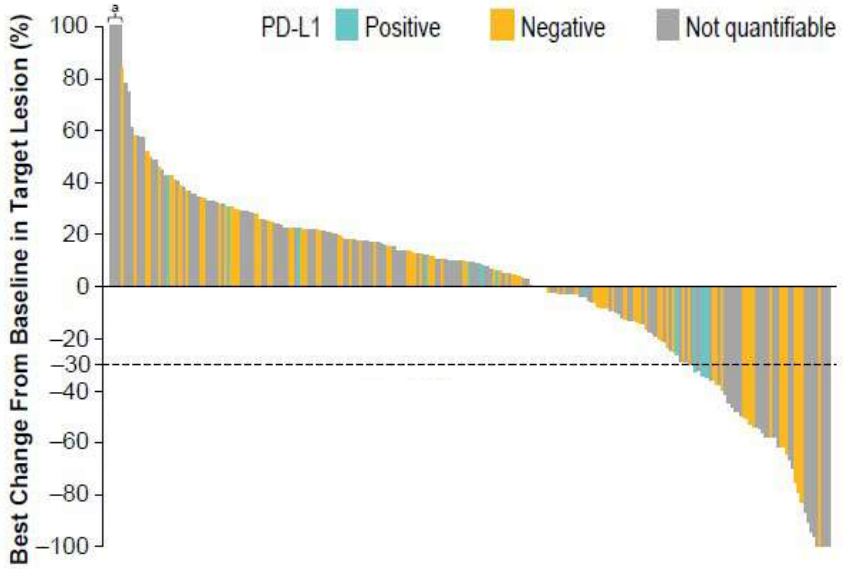


Fuchs CS, et al. JAMA Oncol 2018;4:e180013

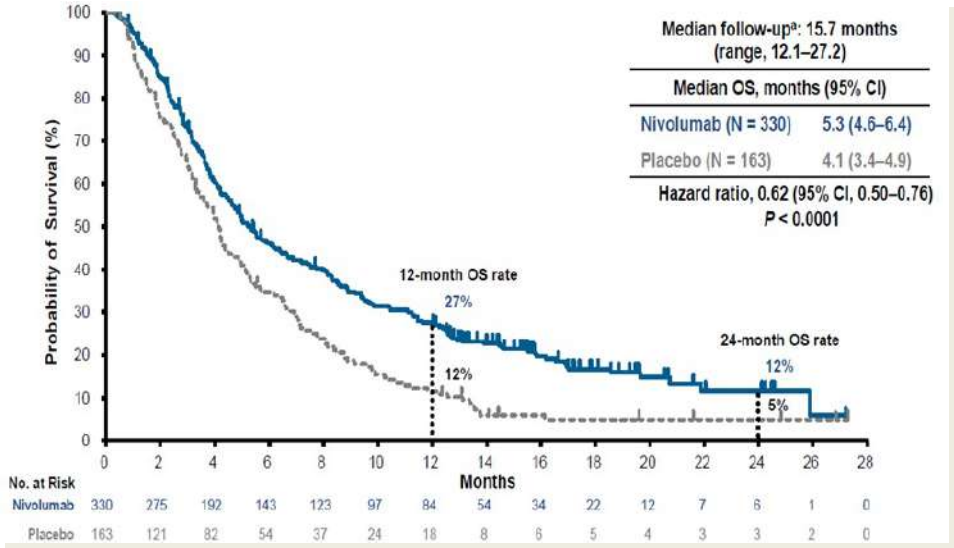
ATTRACTION-2 (phase III)

Nivolumab in chemorefractory mGC

RECIST response rates are modest (12%)
No impact of PD-L1 status



Significant improvement of OS
No impact of PD-L1 status



RECIST, Response Evaluation Criteria In Solid Tumours

Patients from Asia= 100%

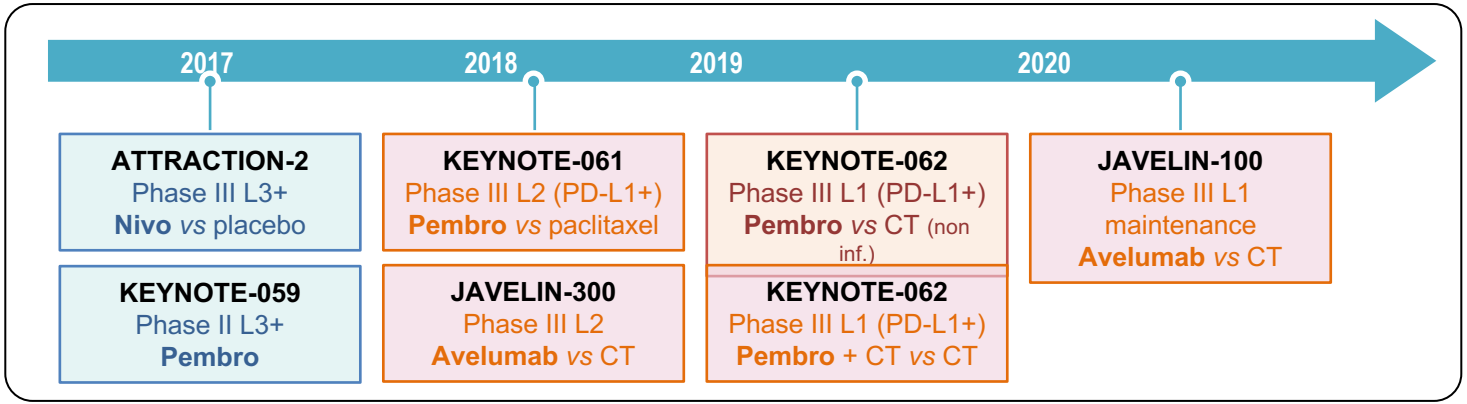
Kang YK, et al. Lancet 2017;390:2461–2471

HOWEVER

Immunothérapie des adénocarcinomes gastriques et de la JOG en L1

- **Chimiothérapie par 5FU platine = standard en L1 des cancers gastriques métastatiques HER2-**
- **SG médiane courte < 12 mois**
- **La majorité des patients hors Asie ne reçoivent qu'une ligne de traitement (40% L2, <20% L3)**

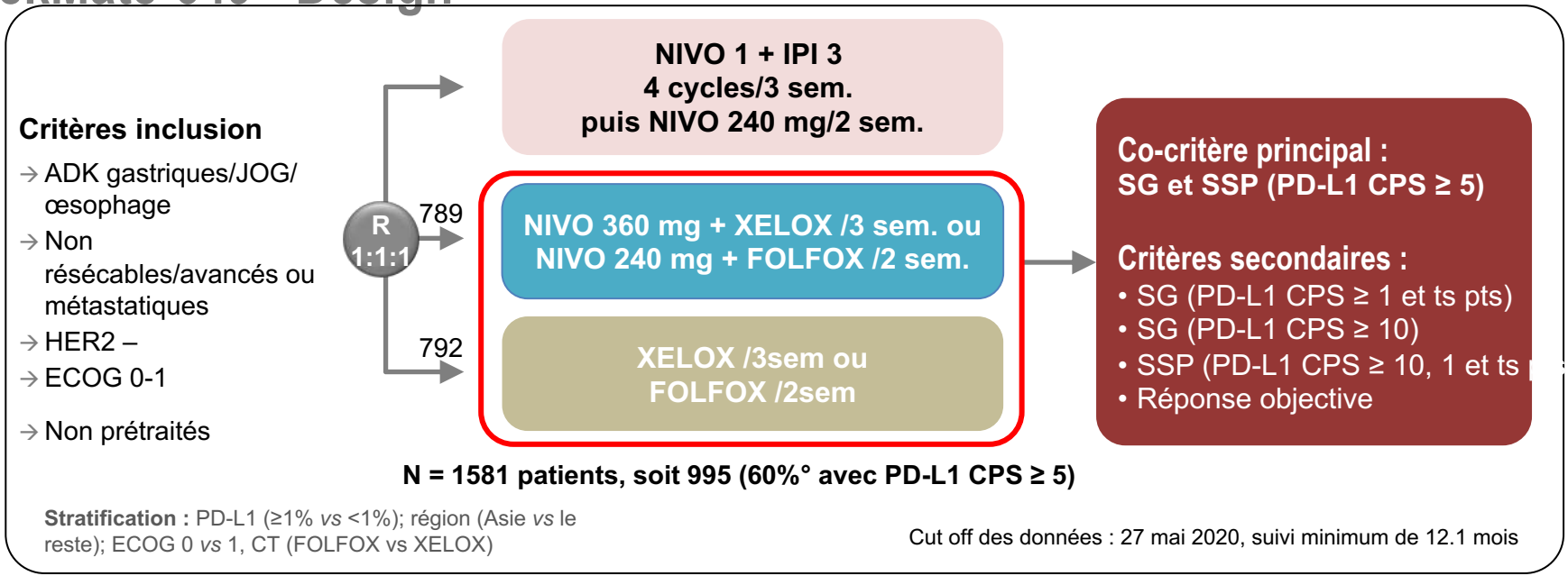
► **Immunothérapie**



- **Étude CheckMate 649**

Nivolumab +/- CT en L1 des ADK œso-gastriques avancés

ChekMate-649 - Design



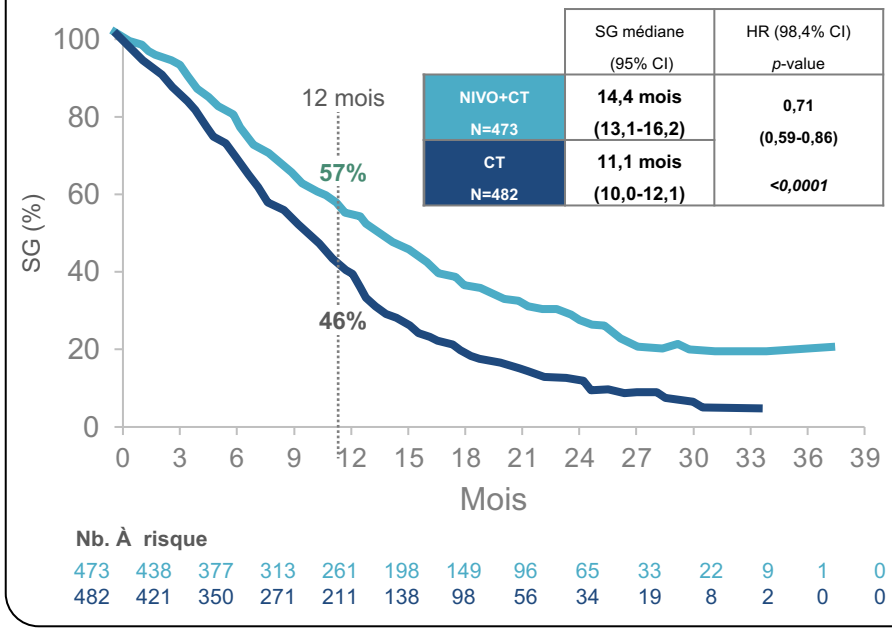
- **2 critères principaux :** SG et SSP chez les patients avec score CPS ≥ 5
- Analyse SG chez patients avec score CPS ≥ 1 si critère principal positif

MH Moehler, et al., ASCO2021, Abs #4002

Nivolumab +/- CT en L1 des ADK œso-gastriques avancés

ChekMate-649 – Rappel SG et SSP pts avec score CPS ≥ 5 (co-critères principaux) (M. Moehler et al., ESMO® 2020, Abs # LB6)

Survie globale

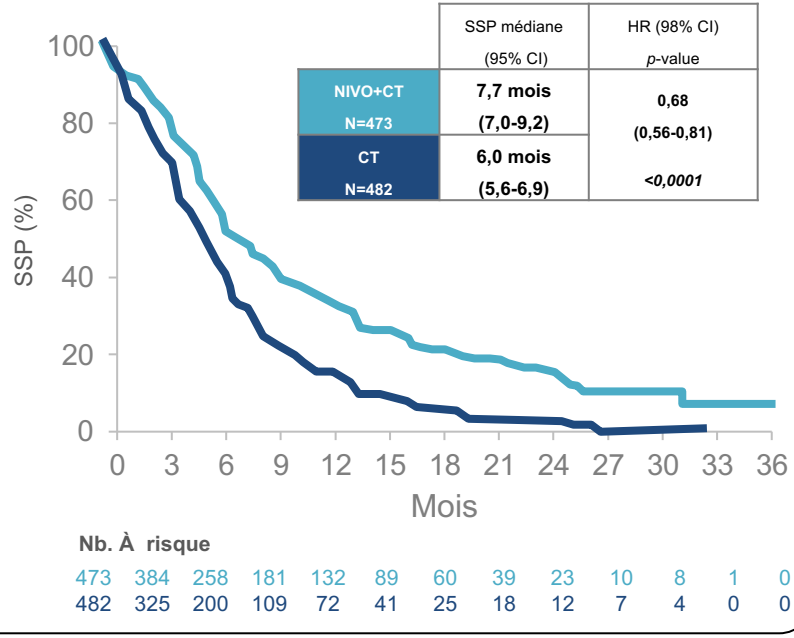


	SG médiane (95% CI)	HR (98,4% CI) *p*-value
NIVO+CT N=473	14,4 mois (13,1-16,2)	0,71 (0,59-0,86)
CT N=482	11,1 mois (10,0-12,1)	*<0,0001*

Nb. À risque

473	438	377	313	261	198	149	96	65	33	22	9	1	0
482	421	350	271	211	138	98	56	34	19	8	2	0	0

Survie sans progression



	SSP médiane (95% CI)	HR (98% CI) *p*-value
NIVO+CT N=473	7,7 mois (7,0-9,2)	0,68 (0,56-0,81)
CT N=482	6,0 mois (5,6-6,9)	*<0,0001*

Nb. À risque

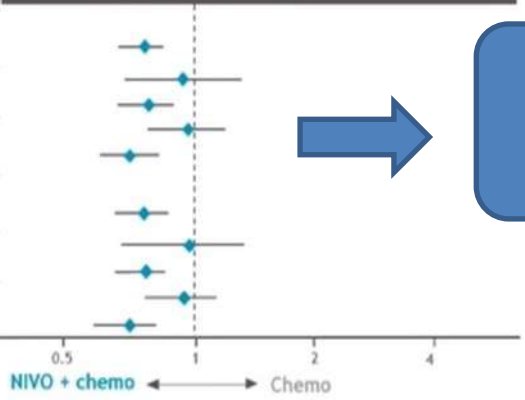
473	384	258	181	132	89	60	39	23	10	8	1	0	
482	325	200	109	72	41	25	18	12	7	4	0	0	

75% de non asiatiques , ORR 58% nivo+CT vs 46% CT

ChekMate-649 – Survie et réponse, analyse en sous-groupes

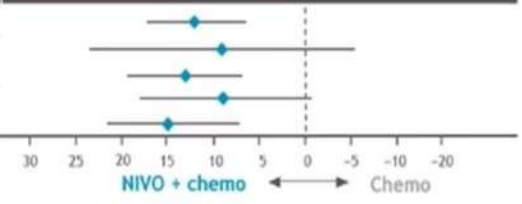
Survival

PD-L1 CPS[a]	Number of patients, n	Median, months		Unstratified HR[b]	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall survival					
Overall (N = 1581)		13.8	11.6	0.79	
< 1	265	13.1	12.5	0.92	
≥ 1	1296	14.0	11.3	0.76	
< 5	606	12.4	12.3	0.94	
≥ 5	955	14.4	11.1	0.70	
Progression-free survival					
Overall (N = 1581)		7.7	6.9	0.77	
< 1	265	8.7	8.1	0.93	
≥ 1	1296	7.5	6.9	0.75	
< 5	606	7.5	8.2	0.93	
≥ 5	955	7.7	6.1	0.69	



Objective response rate

PD-L1 CPS[c]	Number of patients, n	Objective response rate, %		Unweighted ORR difference,[d] %	Unweighted ORR difference,[d] % (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 1211)		58	46	12	
< 1	178	51	41	9	
≥ 1	1019	60	46	13	
< 5	428	55	46	9	
≥ 5	769	60	45	15	



Pas de bénéfice si CPS< 1 ou CPS < 5

KN-811 : Estomac & JOG HER2, intérêt du pembro en L1

- **Standard L1 estomac M+ HER2+** : Chimio (CF) + Trastuzumab (essai ToGA, Bang Lancet 2010)
- **Intérêt de l'immunothérapie + chimio dans les adénoK gastriques avancés HER2 négatifs en L1** : démontré avec le nivo (Attraction 4, Checkmate 649) ; non démontré avec le Pembro (KN-062).
- **Synergie de Pembro + Trastuzumab** ? (2 phases II : Janjigian et al Lancet Oncol 2020;21:821-31 ; Rha et al. JCO 2020 #3081)

Phase III internationale

ADK gastrique et JOG HER2+

- Avancés
- Non prétraités

Stratification :
région, CPS, choix de chimio

R 1:1

N=692

Pembrolizumab
200 mg / 3 sem.
Trastuzumab + Chimio
(FP ou Capox)

Placebo
200 mg / 3 sem.
Trastuzumab + Chimio
(FP ou Capox)

Objectif primaire :

- Survie globale
- Survie sans progression

Objectifs secondaires :

- Taux de réponse
- Durée de réponse
- Tolérance

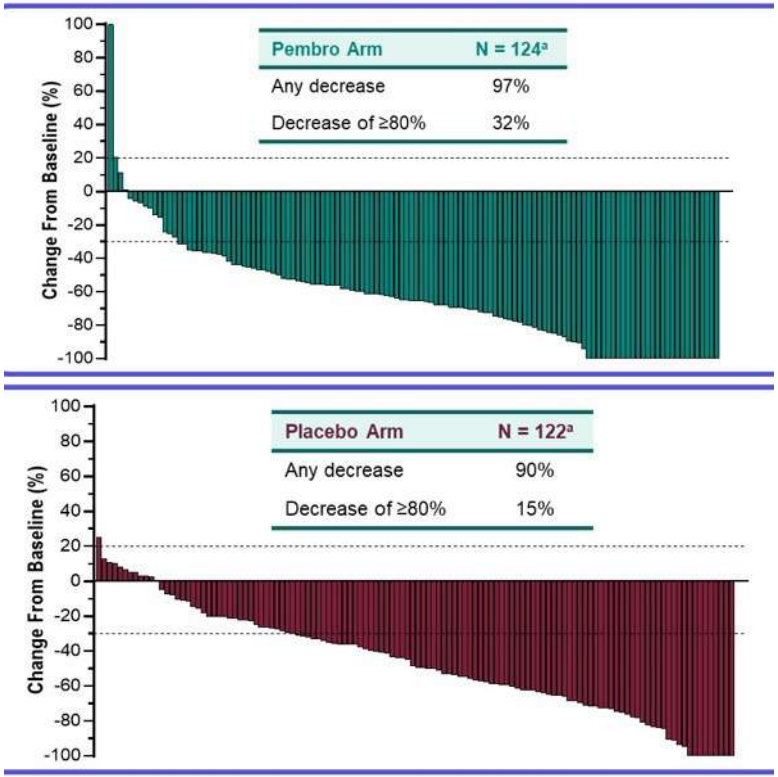
1ère analyse intermédiaire pré-spécifiée
(taux de réponse chez 260 patients avec suivi ≥ 8,5 mois)

KN-811 : Résultats d'efficacité, réponse tumorale objective

Population :

- → **N = 264**, Suivi médian 12 mois (8,5 – 19,4)
- → 62 ans méd, Hommes ~80%, Estomac 70%, Diffus 20%
- → HER2 IHC3+ : 80% / IHC2+ et ISH : 20%
- → **CAPOX : 87% / FP 13%**

	Pembro (n = 133)	Placebo (n = 131)
TRO	**74,4%** [66,2 – 81,6]	**51,9%** [43 – 60,7]
	p = 0,00006	
DCR	96,2%	89,3%
RC	11%	3%
RP	63%	49%
SD	22%	37%
PD	4%	5%
Durée de réponse	Pembro (n = 99)	Placebo (n = 68)
Médiane	**10,6** [1,1+ - 16,5 +]	**9,5 mois** [1,4+ - 15,4 +]
≥ 6 mois	70,3%	61,4%
≥ 9 mois	58,4%	51,1%



Conclusions for immunotherapy in GC

- **There is an activity of IO agents in mGC but the picture is complex !!!**
- **PDL1 expression remains controversial, the best score still needs to be define but CPS is rising (standardization)**
- **MSI and EBV appear to be good markers for IO agents**
- **Nivo + chemo seems to be a new standard first line treatment since ESMO 2020**
- **Ongoing trials (combinations, markers, HER2+ …) will help to better select patients for IO**

What about esophageal cancer ?

Cancer de l'œsophage avancé: CT+/-pembrolizumab KEYNOTE-590 (NCT030189719)

Critères d'inclusion

- Carcinomes épidermoïdes ou ADK de l'œsophage ou de la JOG Siewert 1
- Non prétraités
- ECOG PS 0 ou 1
- Maladie mesurable (RECIST v1.1)

R

1:1

Pembrolizumab 200 mg IV Q3W ≤ 35 cycles
+ CT
5-FU 800 mg/m² IV J1-5 Q3W pour ≤ 35 cycles +
Cisplatine 80 mg/m² IV Q3W pour ≤ 6 cycles

Placebo[a]
+ CT
5-FU 800 mg/m² IV J1-5 Q3W pour ≤ 35 cycles +
Cisplatine 80 mg/m² IV Q3W pour ≤ 6 cycles

Facteurs de stratification:

- Asie *vs* Non-As
- Epidermoïde *vs* ADK
- ECOG PS 0 *vs* 1

Critères principaux :

- SG et SSP (RECIST V1.1, investigator)

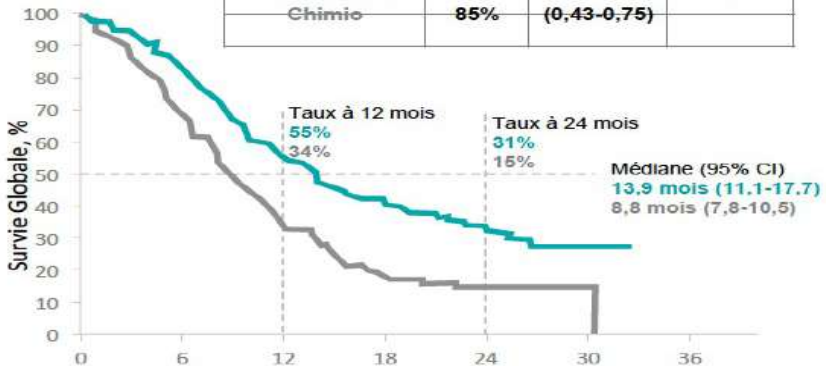
Critères secondaires :

- Taux de réponse (RECIST v1.1, investigator)
- Taux de réponse à 9 semaines (RECIST v1.1, investigator)

Cancer de l'œsophage avancés/ CT+/-pembrolizumab KEYNOTE-590 (NCT030189719) - Survie globale

Epidermoïdes PD-L1 CPS ≥ 10

	Evts	HR (IC 95%)	p
Pembro+Chimio	66%	0,57	< 0,0001
Chimio	85%	(0,43-0,75)	



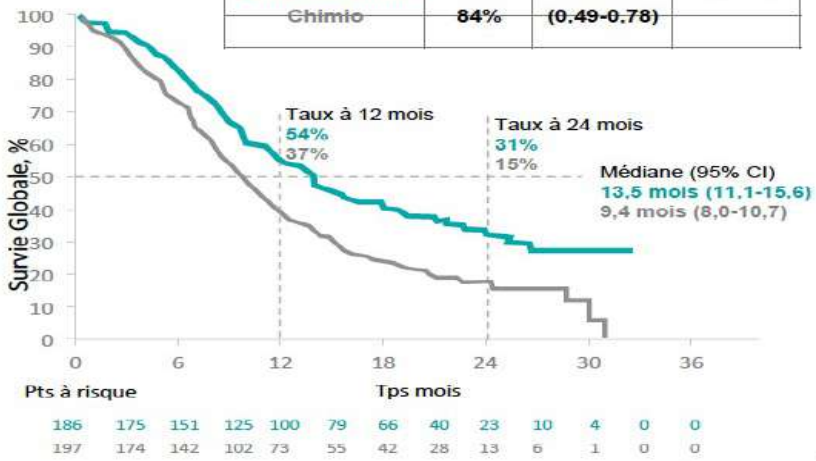
Epidermoïdes (quel que soit CPS)

	Evts	HR (IC 95%)	p
Pembro+Chimio	69%	0.72	0.0006
Chimio	81%	(0.60-0.88)	

Cancer de l'œsophage avancés/ CT+/-pembrolizumab KEYNOTE-590 (NCT030189719) - Survie globale

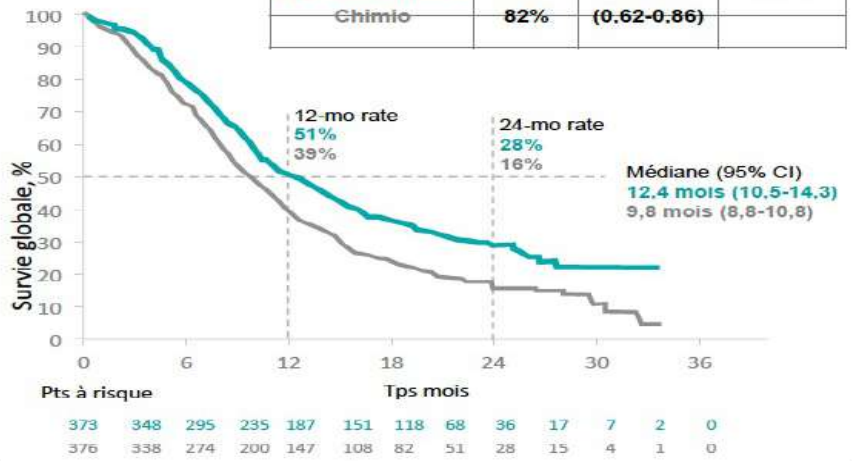
PD-L1 CPS ≥ 10

	Evts	HR (95% CI)	*p*
Pembro+Chimio	67%	0,62	< 0,0001
Chimio	84%	(0,49-0,78)	



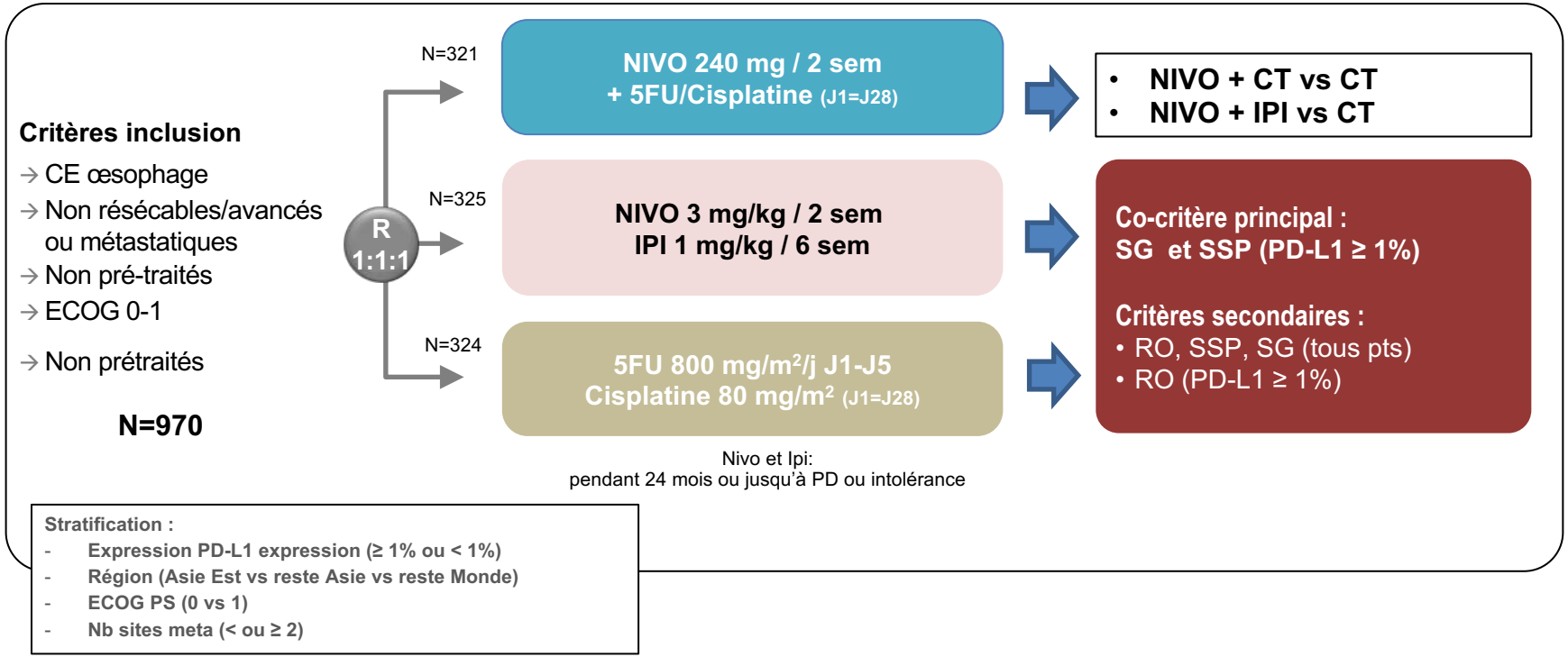
Population globale

	Evts	HR (95% CI)	*p*
Pembro+Chimio	70%	0,73	<0,0001
Chimio	82%	(0,62-0,86)	



Nivolumab en 1ère ligne des épidermoïdes de l'œsophage avancés

ChekMate-648 - Design



- *I Chau et al., ASCO2021, Abs #LBA4001*

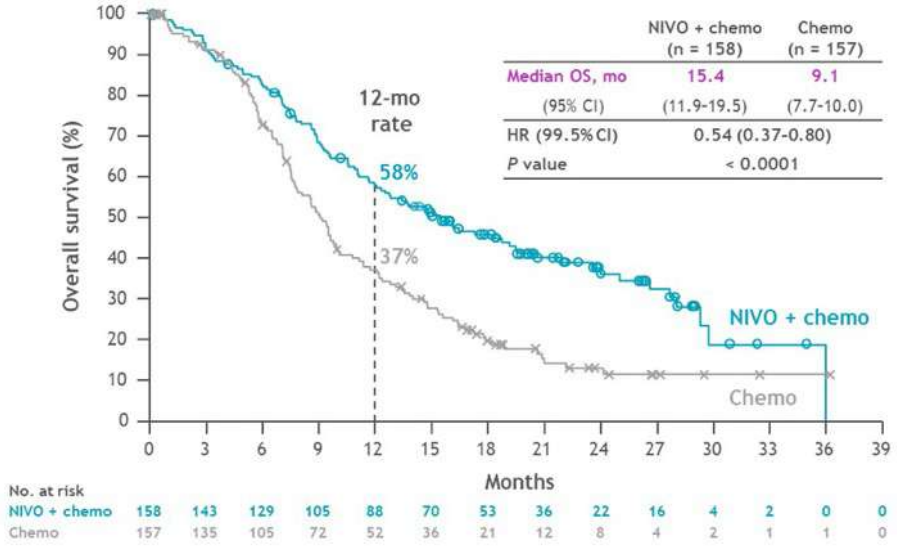
Nivolumab en 1ère ligne des épidermoïdes de l'œsophage avancés

ChekMate-648 – Caractéristiques des patients

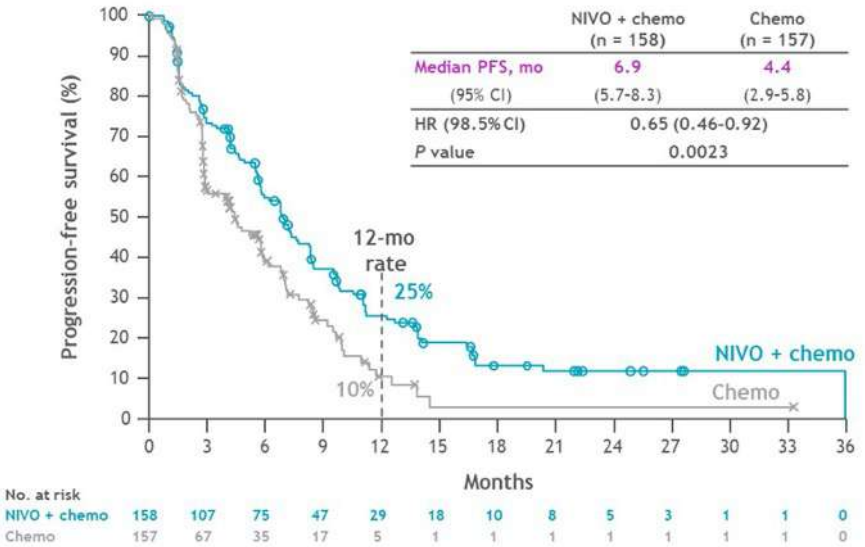
All randomized	NIVO + chemo (n = 321)	NIVO + IPI (n = 325)	Chemo (n = 324)[a]
Median age, years (range)	64 (40-90)	63 (28-81)	64 (26-81)
Male, %	79	83	85
Asian/non-Asian,[b] %	70/30	70/30	70/30
ECOG PS 1,[c] %	54	54	53
ESCC,[d] %	97	99	98
Tumor cell PD-L1 expression,[e] %			
≥ 1%	49	49	48
< 1%	51	51	52
Disease status at study entry, %			
De novo metastatic	57	60	58
Recurrent - locoregional	7	8	8
Recurrent - distant	22	22	19
Unresectable advanced	14	10	16
Number of organs with metastases[f]			
≤ 1	49	49	49
≥ 2	51	51	51
Current or former smoker, %	79	82	79

ChekMate-648 – NIVO + CT vs CT : survie globale et sans progression

SG chez PD-L1 ≥ 1% (critère principal)



SSP chez PD-L1 ≥ 1% (critère principal)

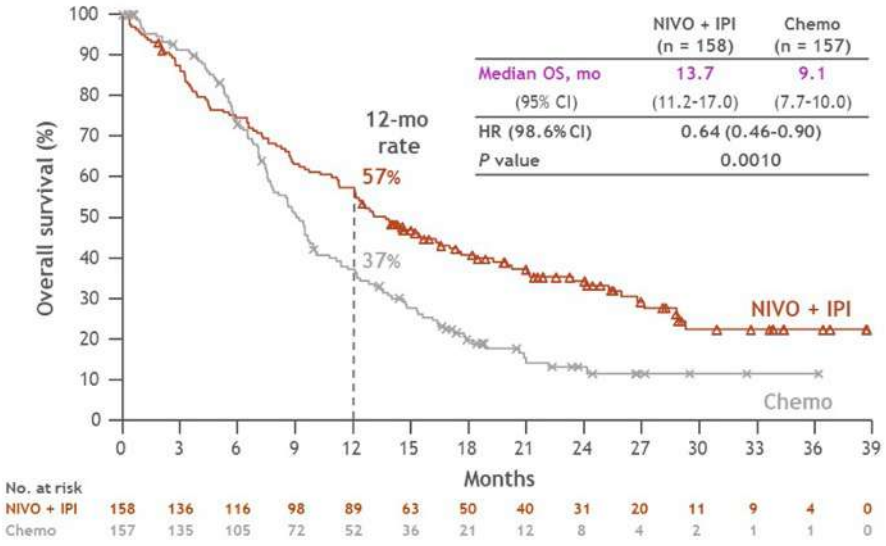


ChekMate-648 – NIVO + CT vs CT : sous groupes

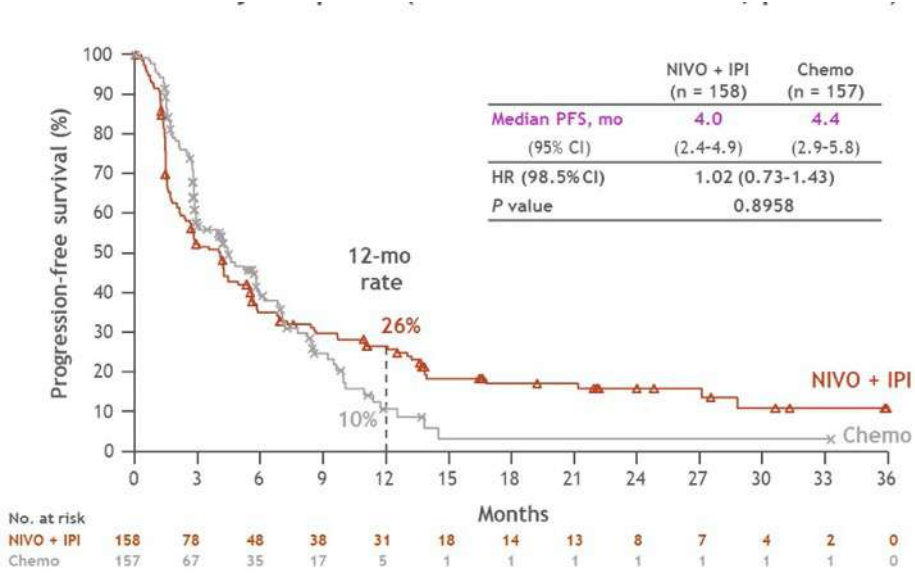
Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death
		NIVO + chemo	Chemo	
Overall (N = 645)		13.2	10.7	0.74
Age, years	< 65 (n = 333)	11.8	10.2	0.80
	≥ 65 (n = 312)	15.1	11.0	0.67
Sex	Male (n = 528)	12.5	10.0	0.70
	Female (n = 117)	15.2	14.8	1.02
Geographic region	Asian (n = 451)	15.5	11.9	0.74
	Non-Asian (n = 194)	10.5	8.5	0.74
ECOG PS[a]	0 (n = 300)	17.3	12.4	0.71
	1 (n = 344)	10.6	9.0	0.76
Tumor cell PD-L1 expression[b]	≥ 1% (n = 314)	15.4	9.2	0.55
	< 1% (n = 329)	12.0	12.2	0.98
	≥ 5% (n = 235)	13.7	9.5	0.61
	< 5% (n = 408)	12.8	11.1	0.82
	≥ 10% (n = 199)	14.7	9.5	0.62
	< 10% (n = 444)	12.3	10.8	0.79
Disease status at study entry	De novo metastatic (n = 371)	13.4	9.4	0.63
	Recurrent - locoregional (n = 46)	14.8	13.5	0.91
	Recurrent - distant (n = 132)	12.3	12.8	1.00
	Unresectable advanced (n = 96)	12.8	12.1	0.73
No. of organs with metastases	≤ 1 (n = 316)	15.7	11.6	0.74
	≥ 2 (n = 329)	11.1	9.6	0.72
Smoking	Current or former (n = 510)	12.3	10.0	0.76
	Never or unknown (n = 135)	15.7	11.1	0.63

ChekMate-648 – NIVO + IPI vs CT survie globale et SSP

SG chez PD-L1 ≥ 1% (critère principal)

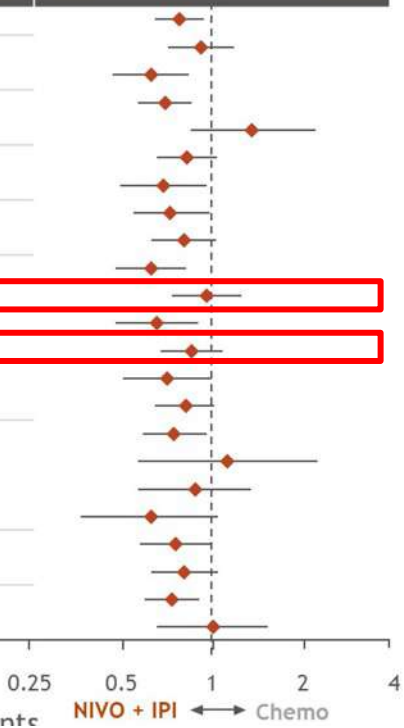


SSP chez PD-L1 ≥ 1% (critère principal)



ChekMate-648 – NIVO + IPI vs CT : sous groupes

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + IPI	Chemo		
Overall (N = 649)		12.8	10.7	0.78	
Age, years	< 65 (n = 351)	12.1	10.2	0.92	
	≥ 65 (n = 298)	16.0	11.0	0.63	
Sex	Male (n = 544)	13.7	10.0	0.70	
	Female (n = 105)	11.7	14.8	1.36	
Geographic region	Asian (n = 455)	13.7	11.9	0.83	
	Non-Asian (n = 194)	11.4	8.5	0.69	
ECOG PS[a]	0 (n = 300)	17.0	12.4	0.73	
	1 (n = 348)	9.7	9.0	0.81	
Tumor cell PD-L1 expression[b]	≥ 1% (n = 314)	13.7	9.2	0.63	
	< 1% (n = 330)	12.0	12.2	0.96	
	≥ 5% (n = 235)	13.0	9.5	0.66	
	< 5% (n = 409)	12.4	11.1	0.86	
	≥ 10% (n = 200)	13.0	9.5	0.71	
	< 10% (n = 444)	12.5	10.8	0.82	
Disease status at study entry	De novo metastatic (n = 383)	12.1	9.4	0.75	
	Recurrent - locoregional (n = 50)	13.9	13.5	1.13	
	Recurrent - distant (n = 133)	15.5	12.8	0.88	
	Unresectable advanced (n = 83)	17.4	12.1	0.63	
No. of organs with metastases	≤ 1 (n = 318)	16.0	11.6	0.76	
	≥ 2 (n = 331)	10.3	9.6	0.81	
Smoking	Current or former (n = 524)	14.4	10.0	0.74	
	Never or unknown (n = 125)	9.8	11.1	1.01	

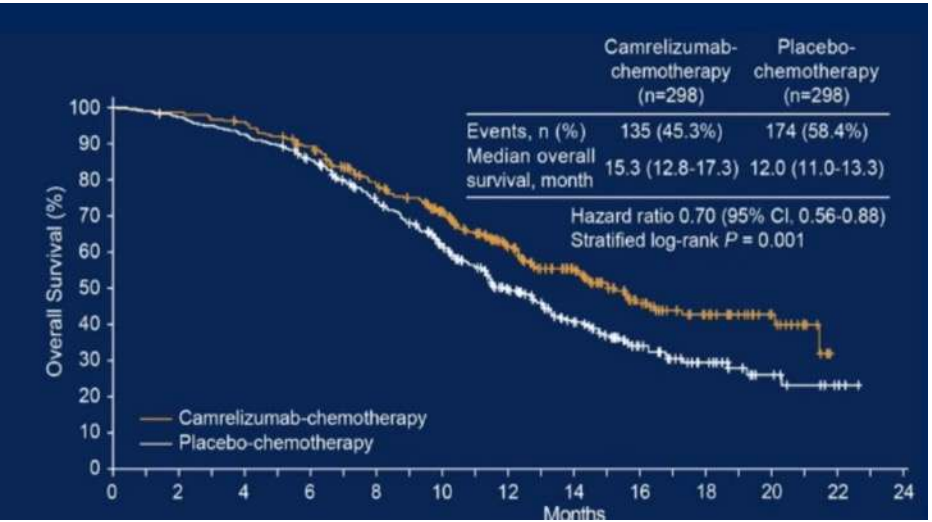


- OS favored NIVO + IPI vs chemo across most prespecified subgroups in all randomized patients

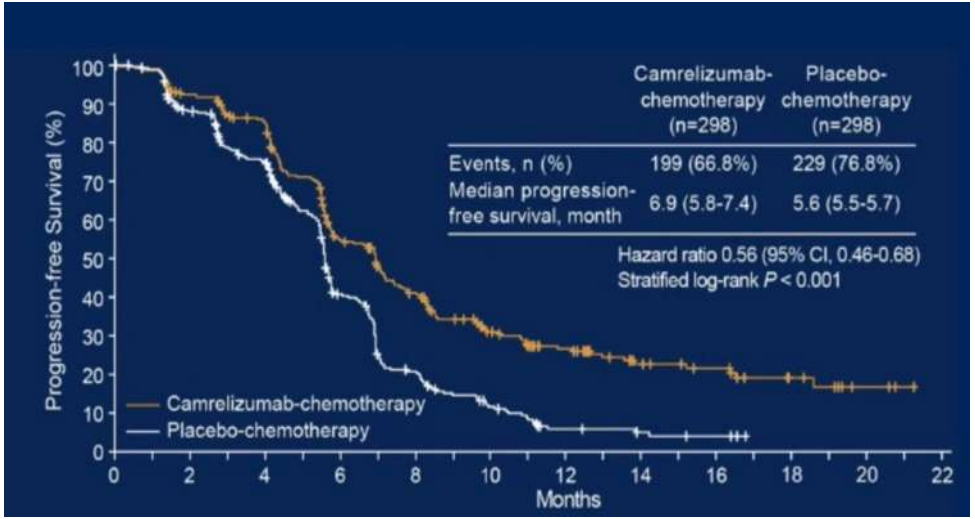
Camrelizumab en L1 des épidermoïdes de l'œsophage avancés

ESCORT-1st – Critères principaux : SG et SSP (revue centralisée)

Survie globale



Survie sans progression



Chimio: par CDDP+ paclitaxel, pas d'analyse selon PDL1 ou CPS

RH Xu, et al., ASCO2021, Abs #4000

Œsophage L2 immuno – essais de phase III

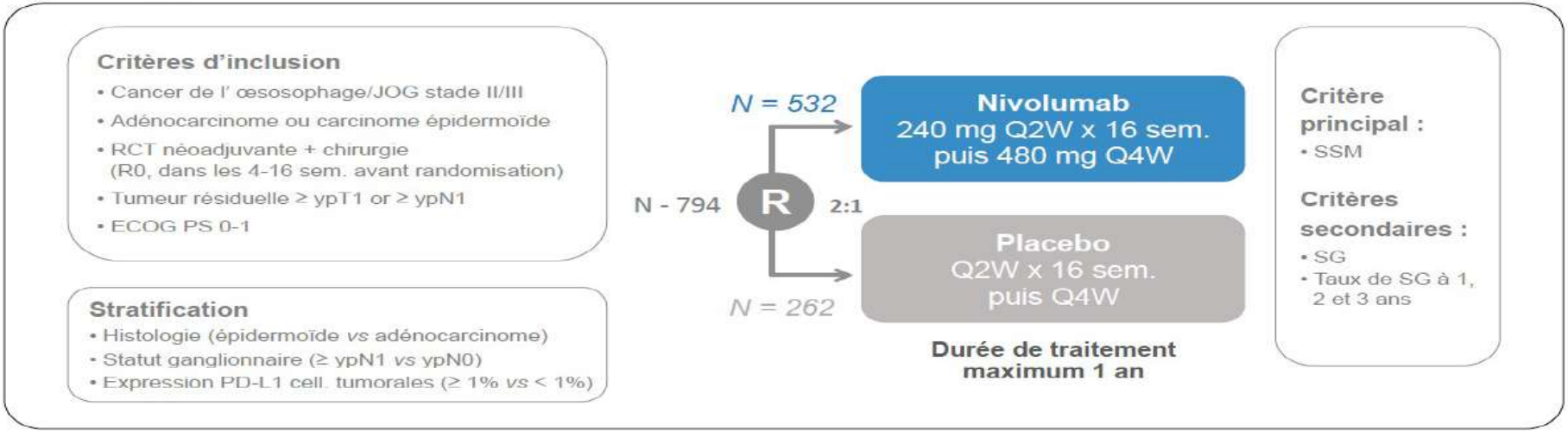
Essai L2	Design	n	Site/histo	%	Asian	Objectif principal	Populations	SG	SSP
Attraction 3	**Nivolumab** *vs* Chimio (taxane)	419	Œso CE	CE : 100%	96%	SG	tous	**Positif HR : 0,77**	Négatif
KN-181	**Pembrolizumab** *vs* Chimio (taxane ou irino)	628	Œso CE ou ADK	CE : 64% ADK : 37%	39%	SG chez CPS≥10 chez CE Population totale	CPS≥10	**Positif HR : 0,69**	**Positif HR : 0,73**
							CE	**Positif HR : 0,78**	Négatif
							Pop totale	Négatif	Négatif
ESCORT	**Camrelizumab** *vs* Chimio (docétaxel ou irino)	457	Œso CE	CE : 100%	100%	SG	Tous	**Positif HR : 0,71**	**Positif HR : 0,69**
RATIONALE 302	**Tislelizumab** *vs* Chimio (taxane ou irino)	512	Œso CE	CE : 100%	79%	SG population totale	pop totale	**Positif HR : 0,70**	Négatif
							CPS ≥ 10	**Positif HR : 0,54**	-

Attraction 3 : Kato K et al, Lancet Oncol 2019
KN-181 : Kojima T et al, JCO 2020
ESCORT : Huang J et al, Lancet Oncol 2020
Rationale 302 : Chen L et al, ASCO 2021 #4012

Nivolumab adjuvant des cancers de l'œsophage ou de la JOG opérés après radiochimiothérapie (RCT)

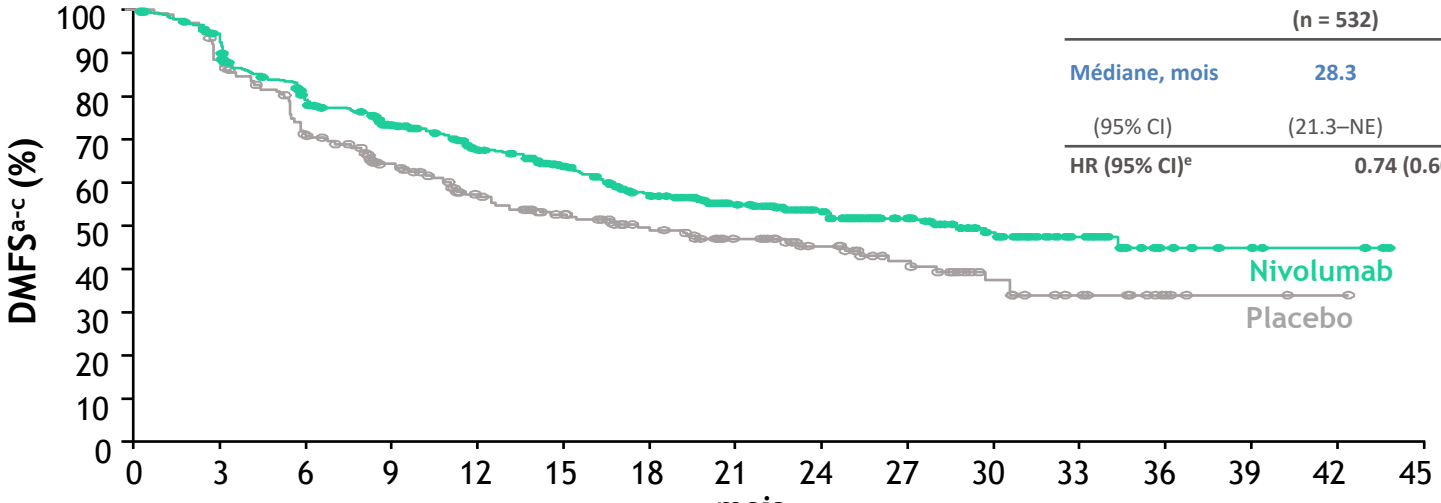
Étude CheckMate 577

Design



Nivolumab adjuvant des cancers de l'œsophage opérés après RCT

ChekMate-577 – Survie sans récidive métastatique



	Nivolumab (n = 532)	Placebo (n = 262)
Médiane, mois	28.3	17.6
(95% CI)	(21.3–NE)	(12.5-25.4)
HR (95% CI)[e]	0.74 (0.60–0.92)	

No. at risk																
Nivolumab	532	449	392	332	276	235	195	160	102	75	44	23	8	4	3	0
Placebo	262	226	180	142	113	93	77	64	46	33	21	14	5	2	1	0

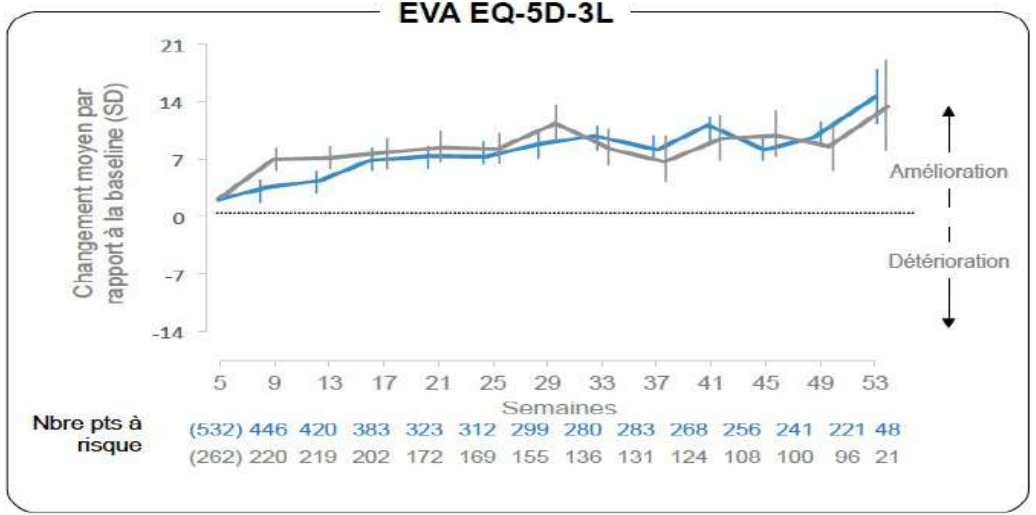
- Taux de récidive à distance (29% vs 39%) et de récidive locorégionale (12% vs 17%) diminués avec le nivolumab

Nivolumab adjuvant des cancers de l'œsophage ou de la JOG opérés après radiochimiothérapie (RCT)

Étude CheckMate 577

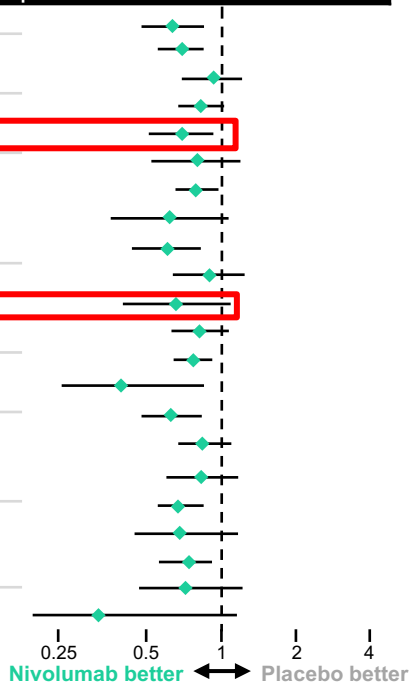
Résultats – Tolérance et Qualité de vie

	Nivolumab N = 532	Placebo N = 260
EI tout grade (%)	376 (71)	119 (46)
EI grade 3-4 (%)	71 (13)	15 (6)
EI graves (%)	40 (8)	7 (3)
EI conduisant à l'arrêt du traitement (%)	48 (9)	8 (3)



ChekMate-577 – Analyse de sous-groupe SSM

Category	Subgroup	Median DFS, mo		Unstratified HR	Unstratified HR (95% CI)
		Nivolumab	Placebo		
Overall	N = 794	22.4	11.0	0.70	
Localisation tumorale	Esophagus (n = 462)	24.0	8.3	0.61	
	Gastroesophageal junction (n = 332)	22.4	20.6	0.87	
Type Histologique	Adenocarcinoma (n = 563)	19.4	11.1	0.75	
	Squamous cell carcinoma (n = 230)	29.7	11.0	0.61	
Expression PD-L1 - % cellules tum.	≥ 1% (n = 129)	19.7	14.1	0.75	
	< 1% (n = 570)	21.3	11.1	0.73	
	Indeterminate/nonevaluable (n = 95)	Not reached	9.5	0.54	
Expression PD-L1 - CPS	≥ 5 (n = 371)	29.4	10.2	0.62	
	< 5 (n = 295)	16.3	11.1	0.89	
	Missing/nonevaluable (n = 128)	Not reached	10.8	0.61	
Envahissement ganglionnaire	ypN0 (n = 336)	Not reached	27.0	0.74	
	≥ ypN1 (n = 457)	14.8	7.6	0.67	
Stade tumoral	ypT0 (n = 47)	34.0	5.2	0.35	
	ypT1 or ypT2 (n = 308)	28.3	9.3	0.60	
	ypT3 or ypT4 (n = 436)	18.9	14.1	0.84	
Temps entre chir et randomisation					
	< 10 weeks (n = 256)	24.0	14.1	0.84	
	≥ 10 weeks (n = 538)	21.4	10.8	0.66	
Dose radiotherapy	< 41.4 Gray (n = 92[d])	19.7	13.8	0.69	
	41.4-50.4 Gray (n = 504)	24.0	11.1	0.73	
	> 50.4 Gray (n = 152)	21.4	8.3	0.72	
	Not reported (n = 41)	14.4	6.1	0.41	

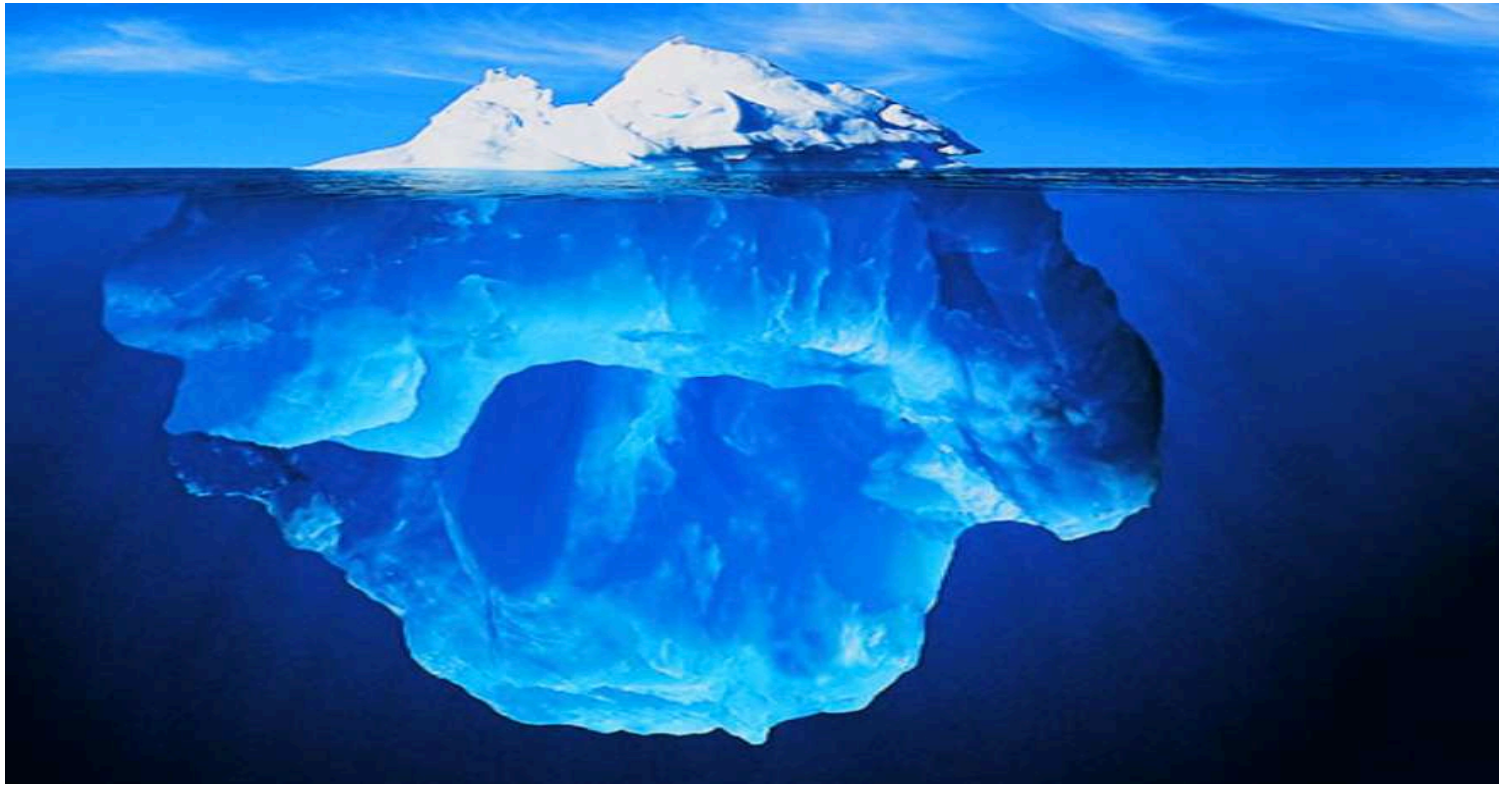


RJ Kelly, et al., ASCO2021, Abs #4003

To conclude

- **Colorectal cancer:**
  - Pembrolizumab a new standard for first line treatment in MSI-H mCRC (KN177)
  - Interesting results in the neoadjuvant setting (NICHE, MDA)
  - no strong signal for MSS (Module, IMBLAZE)
- **Gastric cancer:**
  - Chemotherapy + Nivolumab a standard 1st line in CPS >5 (CM649)
  - Maintenance therapy is not working with immunotherapy (PLATFORM, Javelin Gastric 100)
  - Immunotherapy alone : no strong signal in Caucasians but works in Asians (ATTRACTION, ESCORT…)
- **Esophageal cancer (ESCC and AdK):**
  - Adjuvant Nivolumab the 1st adjuvant treatment for this disease regardless of CPS (CM577)
  - Chemo + pembrolizumab a new standard 1st line in advanced diseases CPS >10 (KN590)
  - Chemo + Nivo a new standard for ESCC in PDL1 >1% (CM648)
  - Immunotherapy is efficient in second line also (KN181, …)
  - Neoadjuvant has to be explored

STILL A LOT OF WORK



THANK YOU