Recherche clinique et rationnel biologique en immunothérapie: **Application aux cancers oesogastriques**

Pr Antoine Adenis

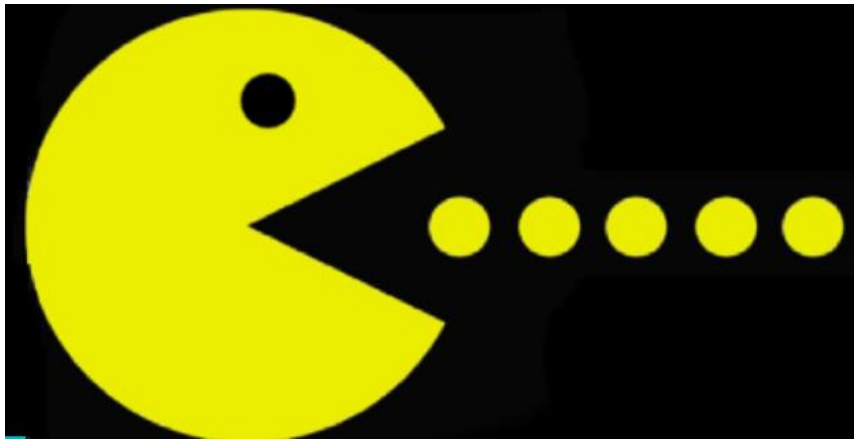
ICM, IRCM-INSERM U1194, SIRIC Montpellier Cancer

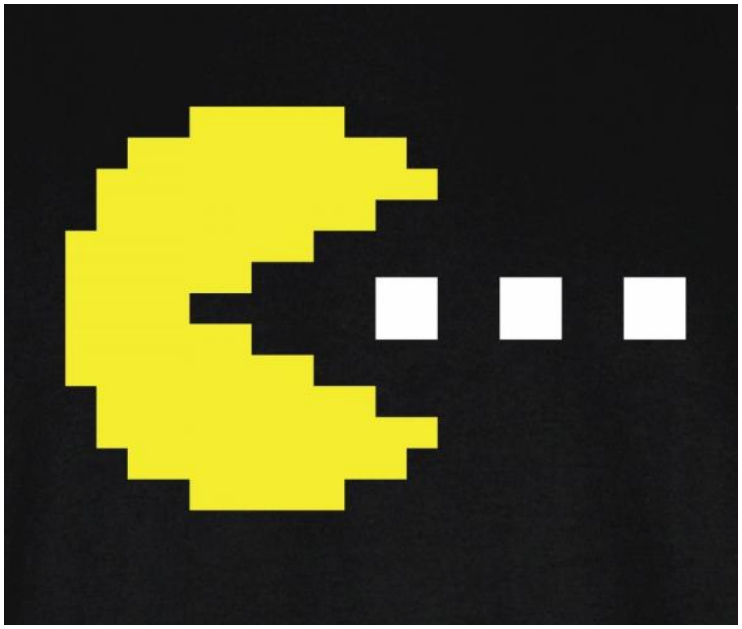
Université Catholique, Lille

How to explain at best how checkpoint inhibitors work, when you are not an immunologist?

- The oncologist way…
  - Our body is able/trained to kill cancer cells by using activated-T cells
  - These T cells are sometimes kept inactive by certain proteins expressed on T cells or tumors. T cells are then unable to kill cancer cells, i.e: cancer cells escape immune surveillance.
  - Checkpoint inhibitors can block these proteins that are expressed on tumor and T cells, allowing then T cells to kill cancer cells…

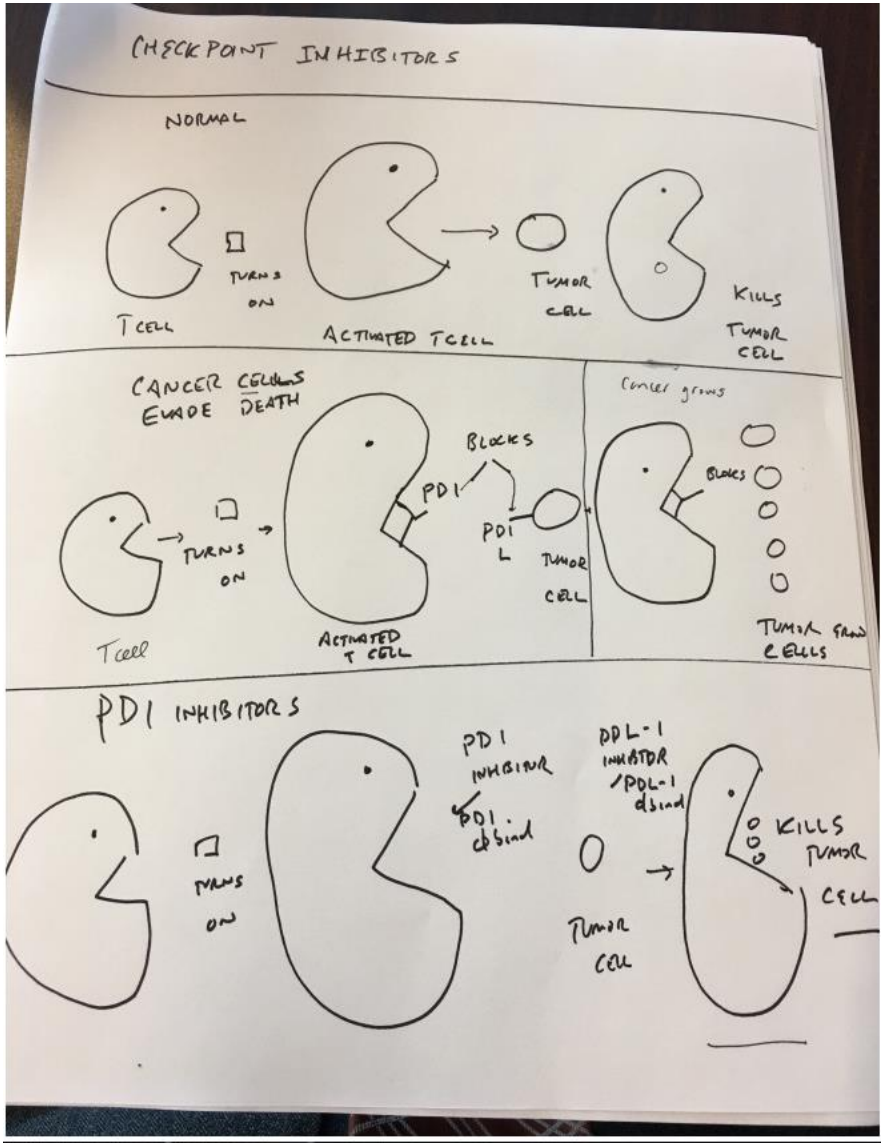
The Pac-Man metaphor…





PAC-MAN, is an arcade game ….released in Japan in May 1980
The player controls Pac-Man through a maze of various dots……
The goal of the game is to consume all the Pac-Dots…..

The Pac-Man metaphor

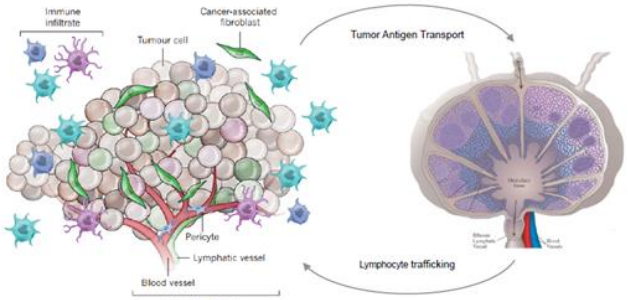


- Think of Pac-Man as the T cell eating up the dots, which are like the cancer cells…
- Checkpoints are expressed and can put a clamp on Pac-Man, and dont let him eat the dots..
- Yet, using checkpoint inhibitors, we can block the clamp and reactivate Pac-Man to eat dots, actually destroying tumor cells.

Mendiratta M, ASCOconnection.org (November 21, 2016)

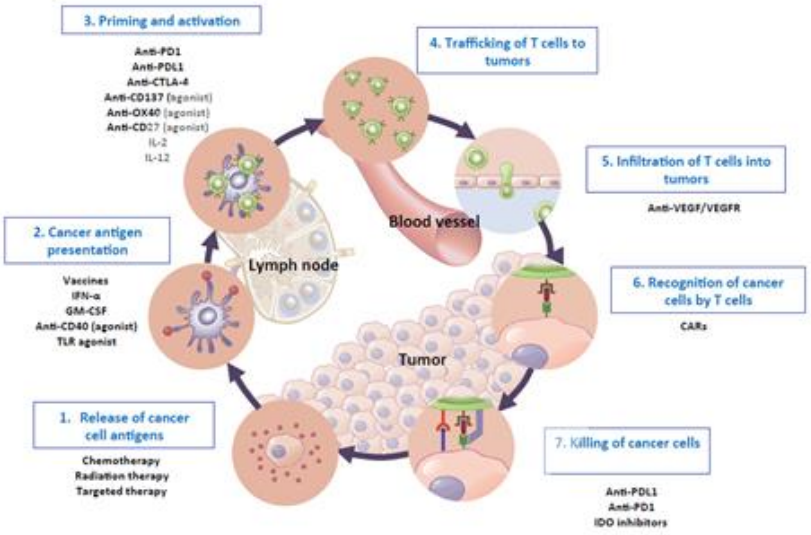
You may also prefer a more complicated way…

- Tumor formation involves the co-evolution of neoplastic cells together with extracellular matrix, tumor vasculature and immune cells.



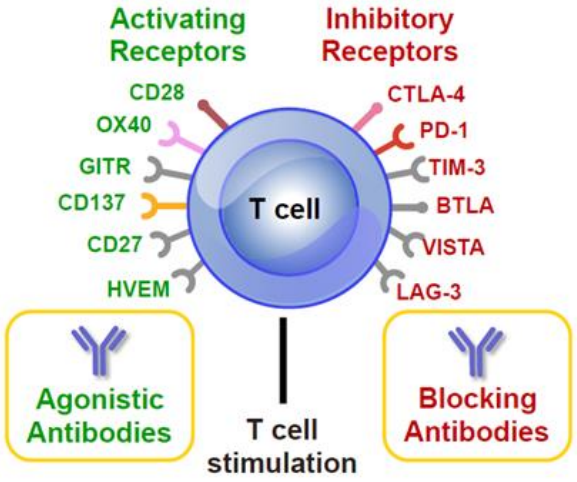
ture 2013

The immune cycle in cancer



Chen, Mellman. Immunity 2013

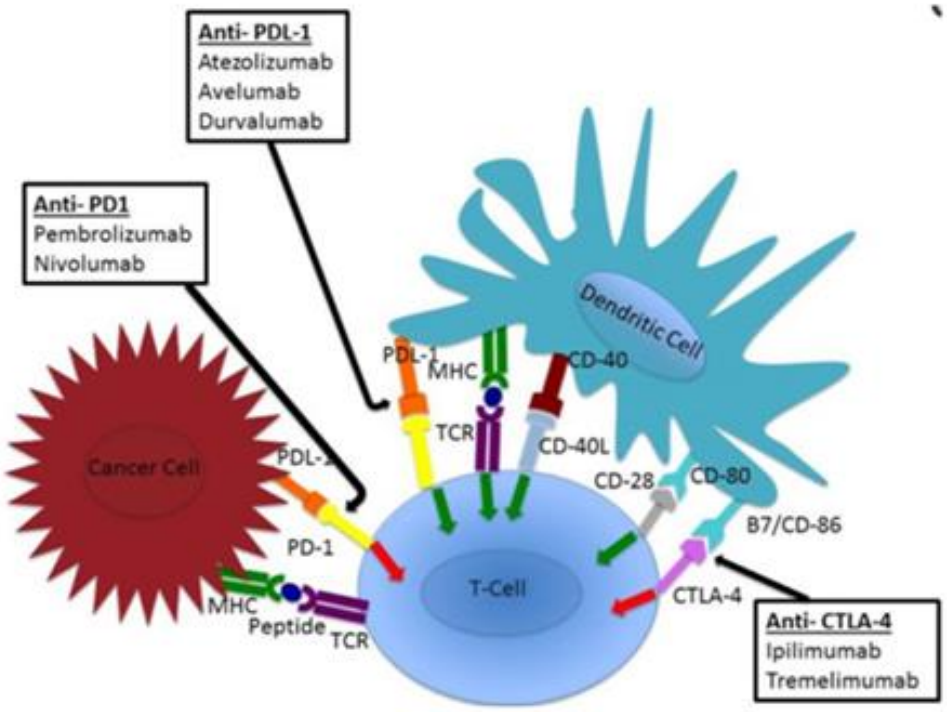
T cell targets for modulating activity



Mellman, Nature 2011

Most common checkpoint inhibitors

PD-1 inhibitors
nivolumab (BMS), pembrolizumab (Merck/MSD)
PDL-1 inhibitors:
avelumab (Pfizer/Merck D), atezolizumab (Roche), durvalumab (AZ)
CTLA4 inhibitors
ipilimumab (BMS), tremelimumab (AZ)



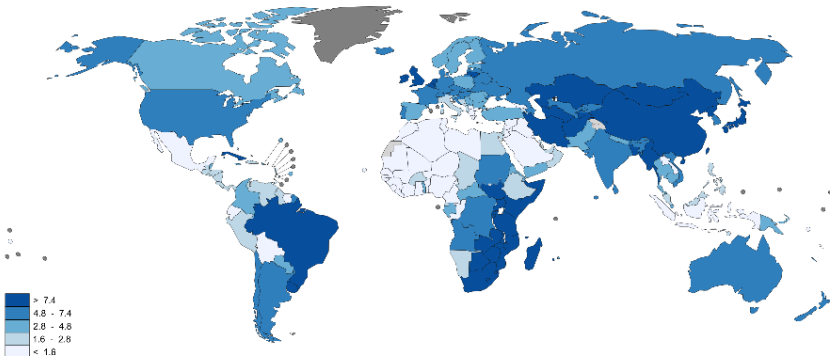
Major breakthrough in advanced malignancies

- **Melanoma**
- **Lung (NSCLC)**
- Urothelial
- Kidney
- Head & Neck
- **MSI tumors (colon, endometrium, gastric,..)**
- Hodgkin disease
- Merckel disease
- HCC
- Anal cancer
- Malignant pleura mesothelioma
- Triple negative Breast cancer

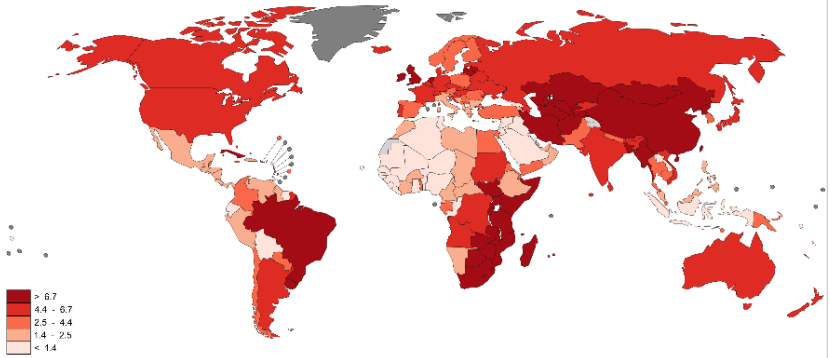
Rationnel

Rationnel Epidémiologique - œsophage

▲ Estimated Oesophageal Cancer Incidence Worldwide in 2012: Men



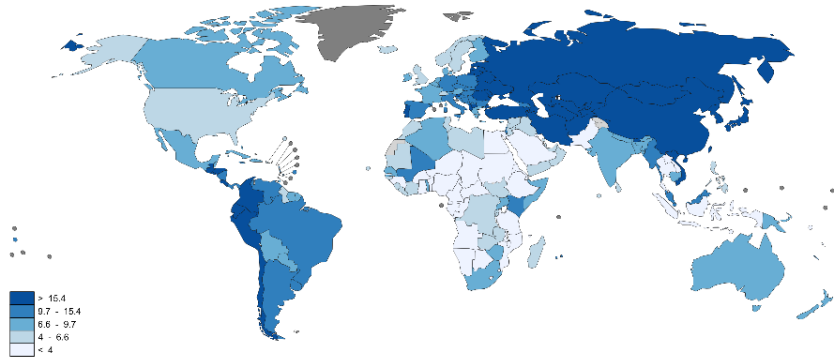
▲ Estimated Oesophageal Cancer Mortality Worldwide in 2012: Men



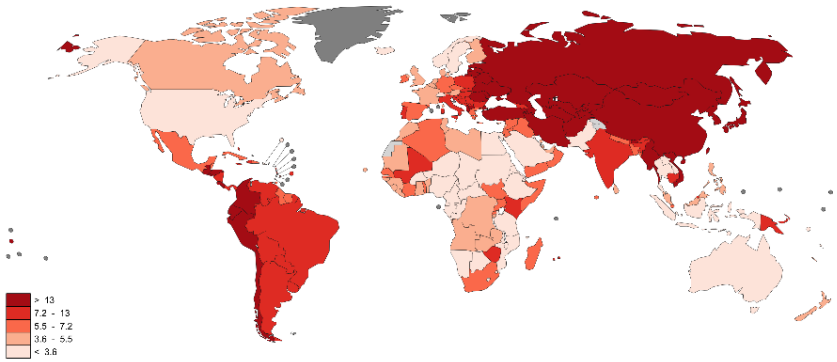
Estimated numbers (thousands)	Men			Women			Both sexes		
	Cases	Deaths	5-year prev.	Cases	Deaths	5-year prev.	Cases	Deaths	5-year prev.
World	323	281	337	133	119	128	456	400	464
More developed regions	68	56	92	18	15	23	86	71	115
Less developed regions	255	225	245	114	104	105	370	329	349
WHO Africa region (AFRO)	14	13	13	10	9	9	23	21	23
WHO Americas region (PAHO)	30	27	35	10	8	11	40	35	46
WHO East Mediterranean region (EMRO)	9	8	8	8	7	8	17	16	16
WHO Europe region (EURO)	39	34	40	14	12	14	53	47	54
WHO South-East Asia region (SEARO)	44	40	31	23	22	17	67	62	48
WHO Western Pacific region (WPRO)	187	159	209	68	61	70	255	219	279
IARC membership (24 countries)	101	85	115	36	31	34	137	116	149
United States of America	13	13	17	4	3	4	17	16	21
China	160	140	162	63	57	61	223	197	222
India	27	25	14	15	14	8	42	39	22
European Union (EU-28)	26	22	29	9	7	9	35	30	38

Rationnel Epidémiologique - estomac

▲ Estimated Stomach Cancer Incidence Worldwide in 2012: Men



▲ Estimated Stomach Cancer Mortality Worldwide in 2012: Men



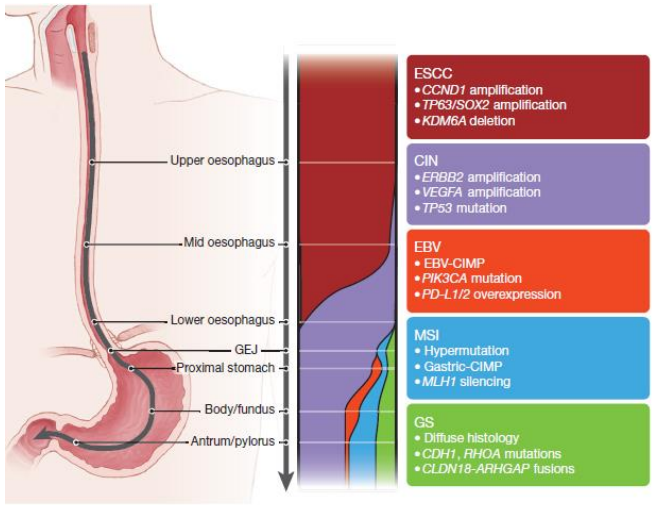
Estimated numbers (thousands)	Men			Women			Both sexes		
	Cases	Deaths	5-year prev.	Cases	Deaths	5-year prev.	Cases	Deaths	5-year prev.
World	631	469	1031	320	254	507	952	723	1538
More developed regions	175	107	372	99	68	193	275	175	565
Less developed regions	456	362	659	221	186	315	677	548	974
WHO Africa region (AFRO)	10	10	14	9	8	12	19	18	26
WHO Americas region (PAHO)	52	39	84	34	26	54	85	65	138
WHO East Mediterranean region (EMRO)	15	13	19	9	8	11	23	21	31
WHO Europe region (EURO)	98	75	136	64	51	86	162	126	222
WHO South-East Asia region (SEARO)	60	56	54	30	28	29	91	83	82
WHO Western Pacific region (WPRO)	396	276	724	175	134	315	571	410	1039
IARC membership (24 countries)	232	148	449	124	86	226	355	234	675
United States of America	13	7	20	8	5	12	21	12	32
China	283	221	419	122	104	175	405	325	594
India	43	41	31	20	18	14	63	59	45
European Union (EU-28)	51	35	74	31	23	45	82	58	119

Connexions between immune status and Esophageal/Esogastric cancers

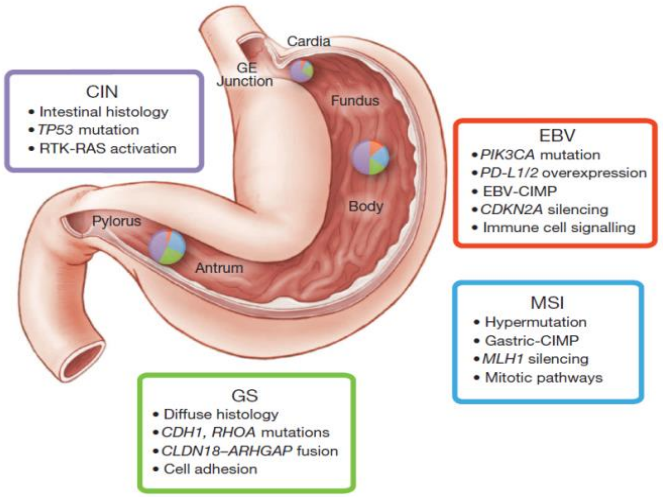
- PD-L1, and PD-L2 are expressed in Esophageal and in Esogastric tumors, and their expression is correlated with poor prognosis (even after multivariate analysis)
- High level of TILs in gastric cancer (subtypes ukn)
- Presence of immune stimulatory factors such as EBV and microsatellite instability in some gastric cancers

Grogg, Mol Pathol 2003; Mizukami, Br J Cancer 2008; Lee, Br J Cancer 2008; Thompson, Gut 2016; Ohigashi, Clin Cancer Res 2005; Loos, Ann Thoracic Surg 2011; Wu, Acta Histochem 2006; Derks, Cancer Immunol Res 2015; The Cancer Genome Atlas Research Network, Nature 2014

Classification moléculaire
et sensibilité potentielle à l'immunothérapie



- Oeso SCC lookS like SCC of other organs.
- No evidence for an aetiological role of HPV
- Oeso SCC showed genomic amplifications of CCND1, and SOX2
- **Chimiosensibilité**
- **Signature « tabac » chez certaines tumeurs**
- Oeso ADK strongly resembled the CIN gastric ADK,



9% des cancers gastriques
Amplification de CD274 et PDCD1LG2 qui codent PDL1 et PDL2

4-20 % des cancers gastriques

The Cancer Genome Atlas Research Network
Nature 2014 & 2017

Rationnel: Les besoins non satisfaits !

oesophage

- Localisé SCC: SV5 30%
- Localisé ADK: SV5 40%
- Méta: 10-12mo

estomac

- Localisé: SV5 30%
- Méta: 10-16mo

Cancers métastatiques

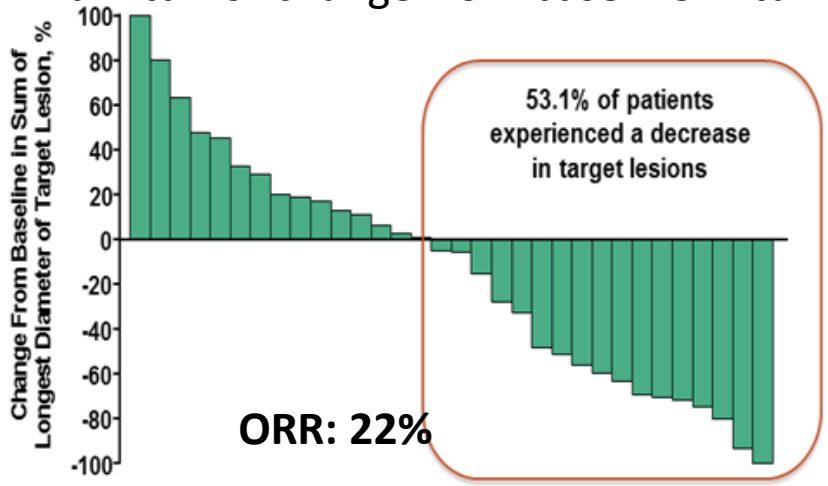
PD1-inhibitors

Pembrolizumab

Keynote 012 (phase 1b, estomac),
Keynote 059 (phase 2 multi-bras, estomac),
Keynote 028 (phase 2, œsophage)

KEYNOTE 012 trial
Gastric cohort

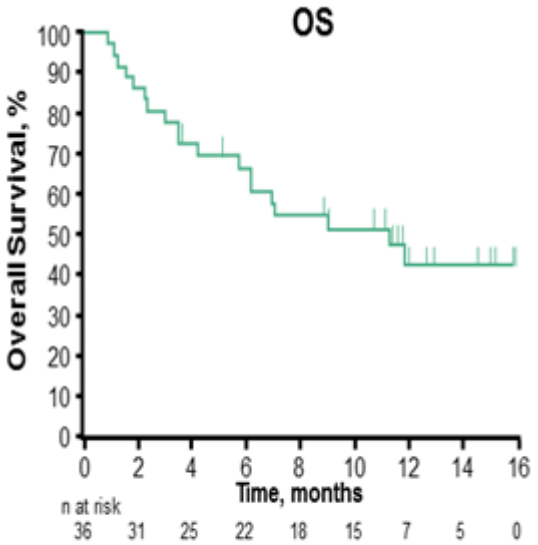
Maximum tumor change from baseline in tumor size



Median time to response : 8 wks
Median duration time: 40 wks

Severe AEs: 13%

- Phase 1b
- Pembrolizumab 10mg/kg, Q 2w
- N=39 pts in the gastric cohort
- PD-L1 status looking at tumor & immune cells
- 66% heavily pretreated (≥ 2 lines)



- 6-month OS rate: 66%
- Median OS: 11.4 months (95% CI, 5.7-NR)

Muro, Lancet Oncol 2016

KEYNOTE-059: Gastric/EGJ Cancer

A phase 2 trial

Cohort 1 Patients • ≥ 2 prior lines of chemotherapy	**Pembrolizumab 200 mg Q3W**	Fuchs, ASCO 2017 Wainberg, ESMO 2017
Cohort 2 Patients • No prior therapy	**Pembrolizumab 200 mg Q3W + cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2 Q3W or capecitabine 1000 mg/m^2 BID Q3W[3]**	Bang, ASCO 2017 Wainberg, ESMO 2017
Cohort 3 Patients • No prior therapy • PD-L1 positive	**Pembrolizumab 200 mg Q3W**	Wainberg, ESMO 2017

Pembrolizumab monothérapie (KEYNOTE-059 cohorte 1)

- N=259
- Highly Pretreated patients
- L3: 52%, L4 48%
- PD-L1 status: all comers
- PD-L1+ (≥ 1% tumor & immune cells): 52%

- ORR: 11,6% (6% in L4)
- Median response duration: 8.1 mo
- PDL1+ : 15.5% and PDL1-: 6.1%
- MSI + (n=7): 57%, MSI-: 9%

- OS: 5.6 mo ; 1 yr = 23,4%

Fuchs, ASCO 2017

KEYNOTE-059: Gastric/EGJ Cancer

A phase 2 trial

Cohort 1 Patients • ≥ 2 prior lines of chemotherapy	**Pembrolizumab 200 mg Q3W**	Fuchs, ASCO 2017 Wainberg, ESMO 2017
Cohort 2 Patients • No prior therapy	**Pembrolizumab 200 mg Q3W + cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2 Q3W or capecitabine 1000 mg/m^2 BID Q3W[3]**	Bang, ASCO 2017 Wainberg, ESMO 2017
Cohort 3 Patients • No prior therapy • PD-L1 positive	**Pembrolizumab 200 mg Q3W**	Wainberg, ESMO 2017

Pembrolizumab plus FU-CDDP (KEYNOTE-059 cohorte 2)

- 25 patients
- ADK gastrique ou cardia M+ HER2 nég. En 1ère ligne

ADK gastrique
1ère ligne

↔

Pembro 200 mg
Cisplatine
80 mg/m² + **5FU** 800 mg/m²
/ 3 semaines x 6 cycles

Critère de jugement : taux de réponse

- PD-L1+, n = 16
- PD-L1 nég, n = 8
- ND = 1

Pembrolizumab plus FU-CDDP (KEYNOTE-059 cohorte 2)

Table 5. Grade 3/4 Treatment-Related Adverse Events

Event	Grade 3/4 n (%)
Neutropenia[a]	16 (64)
Stomatitis	5 (20)
Anemia	2 (8)
Decreased appetite	2 (8)
Fatigue	2 (8)
Palmar-plantar erythrodysesthesia syndrome	2 (8)
Thrombocytopenia[b]	2 (8)
Decreased WBC count	1 (4)
Febrile neutropenia	1 (4)
Nausea	1 (4)
Maculopapular rash	1 (4)
Pyrexia	1 (4)
Decreased weight	1 (4)
Hypophosphatemia	1 (4)

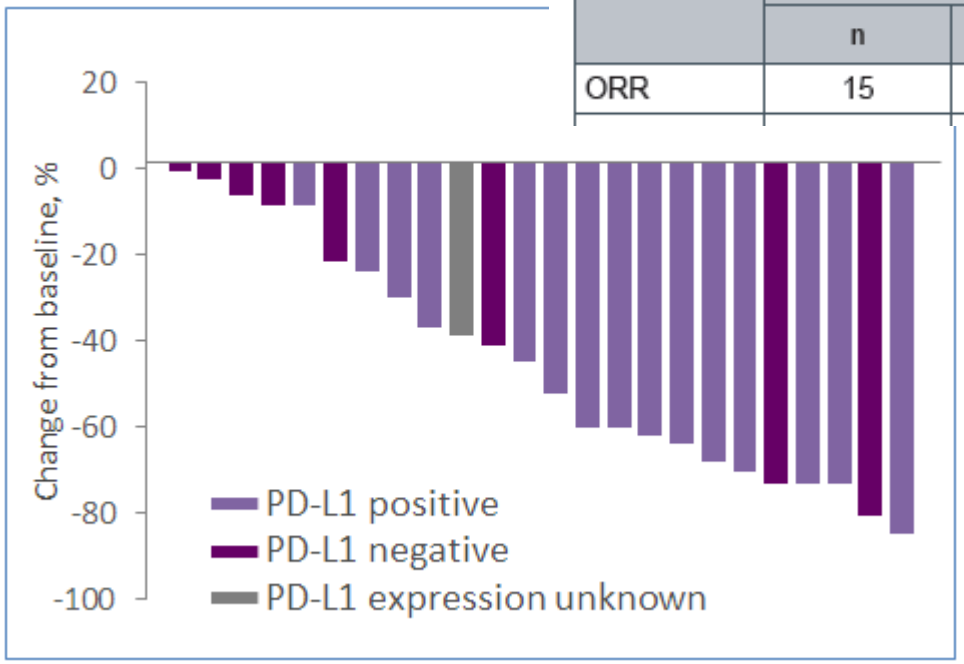
76% of severe AEs, including
16% of immunologic AEs

Bang, ASCO 2017

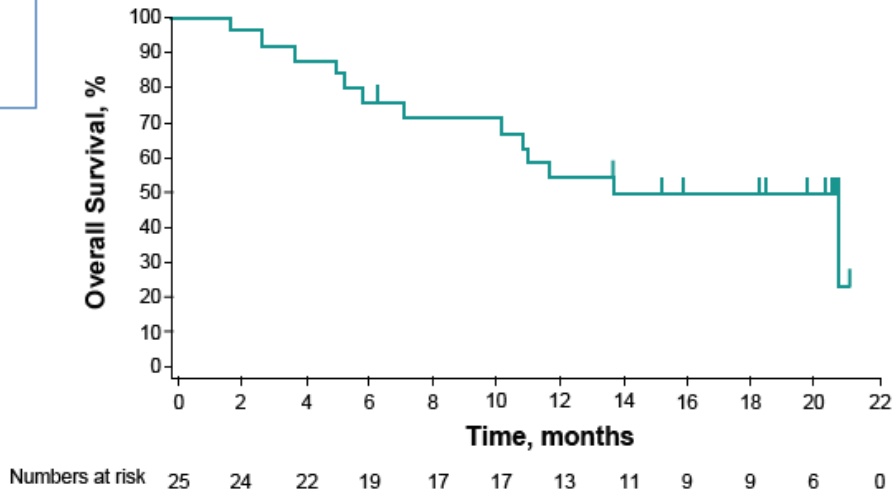
- ORR was 60% (95% confidence interval [CI], 39-79) in the total population (**Table 3**)

Table 3. Response[a] Assessed by Central Review per RECIST v1.1

	Total N = 25		PD-L1 Positive n = 16		PD-L1 Negative n = 8	
	n	% (95% CI[b])	n	% (95% CI[b])	n	% (95% CI[b])
ORR	15	60 (39-79)	11	69 (41-89)	3	38 (9-76)



Bang, ASCO 2017; Wainberg, ESMO 2017



Median OS: 21 mo

KEYNOTE-059: Gastric/EGJ Cancer

A phase 2 trial

Cohort 1 Patients • ≥ 2 prior lines of chemotherapy	**Pembrolizumab 200 mg Q3W**	Fuchs, ASCO 2017 Wainberg, ESMO 2017
Cohort 2 Patients • No prior therapy	**Pembrolizumab 200 mg Q3W + cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2 Q3W or capecitabine 1000 mg/m^2 BID Q3W**[3]	Bang, ASCO 2017 Wainberg, ESMO 2017
Cohort 3 Patients • No prior therapy • PD-L1 positive	**Pembrolizumab 200 mg Q3W**	Wainberg, ESMO 2017

Pembro monothérapie 1ere ligne (KEYNOTE-059 cohorte 3)

- 31 patients
- ADK gastrique ou cardia métastatiques

ADK gastrique M+
1ère ligne
PDL 1 +
HER 2 -

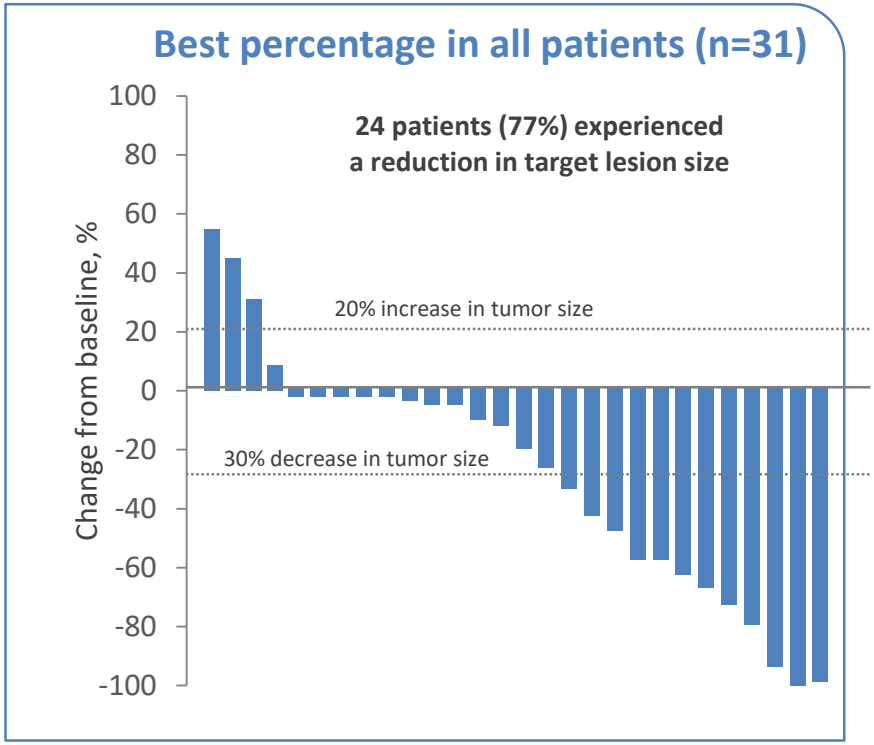
↔

Pembro 200 mg
monothérarapie

Critère de jugement : taux de réponse

Wainberg, ESMO 2017

Pembro monothérapie 1ere ligne (KEYNOTE-059 cohorte 3)



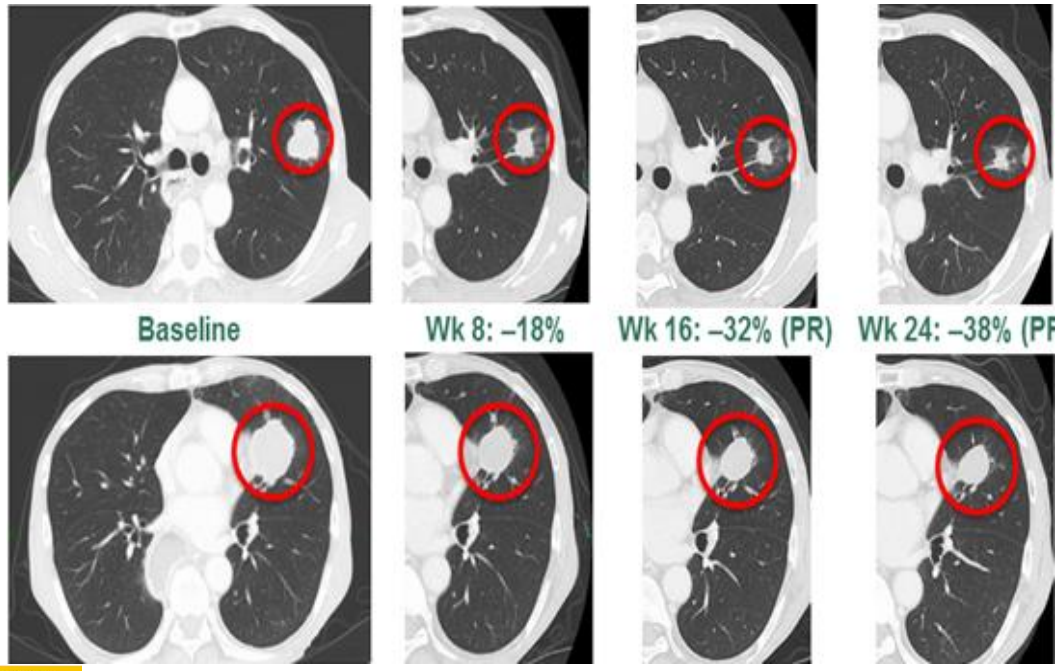
- Taux de réponses : **26%** (RC : **7%**)

- durée de réponse : 9.6 mois
- SSP médiane 3.3 mois,
- SG médiane 20.7 mois
- toxicités sévères: 23%

Keynote-028:Pembrolizumab for patients with advanced esophageal cancer

- N=23, 8% ≥ 3 lines, 74% SCC
- Pembro 10mg/kg, every 2wks
- ORR 30% (ADK 40%, SCC 29%)
- Median response duration: 40wks

Doi, ASCO 2015



Principales études PEMBROLIZUMAB dans les cancers de l'œsophage et de l'estomac métastatiques

étude	Tumeur	traitements	Ligne	statut
Keynote-181	Estomac/JOG	Pembro vs DCT/IRI/PCT	2ème ligne	terminée
Keynote-061	Estomac/JOG	Pembro vs PCT	2ème ligne	terminée
Keynote-062	Estomac/JOG	Pembro vs FU-CDDP- Pembro vs FU-CDDP-Pbo	1ère ligne	en cours
Keynote-590	Œsophage (ADK, SCC)	Pembro-FU-CDDP vs Pbo-FU-CDDP	1ère ligne	T4 - 2017

PD1-inhibitors

Nivolumab

ONO 45-38/07

Checkmate 032

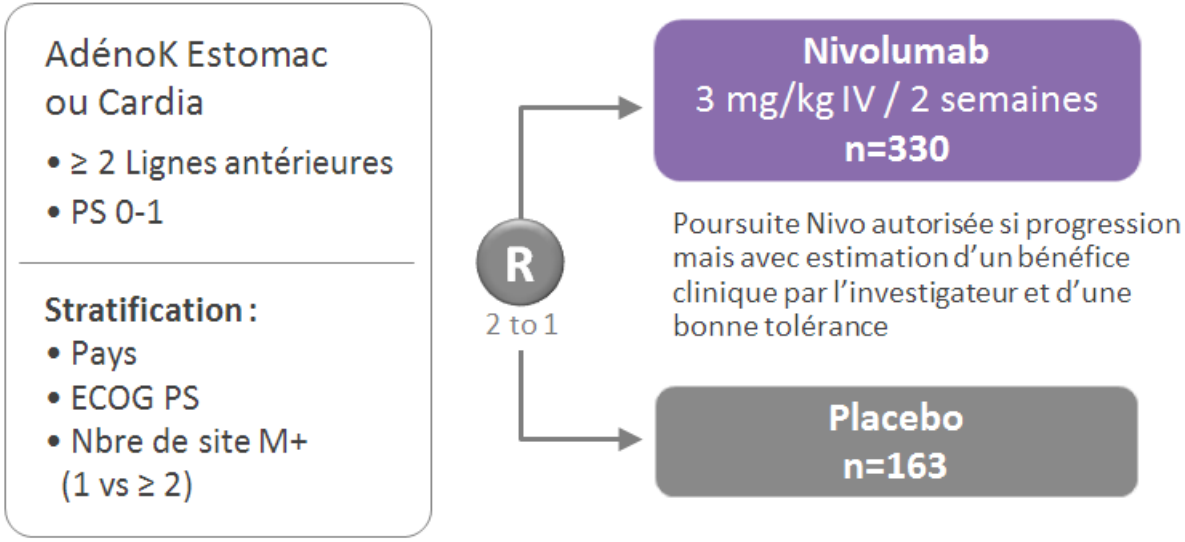
ONO 12 Attraction

Nivolumab monothérapie et cancer de l'oesophage

Items	ONO 45-38/07	Checkmate 032 Cohort Nivo 3 mg/kg
indications	SCC	ADK E/EGJ/G
n	64	59
region	japan	US/EU
Prior systemic therapy	68% > 2nd line	83% > 1stline
ORR (PD-L1+/-)	17% (24%/13%)	14% (27%/12%)
mDOR	-	7
mPFS	1.5 mo	1.4 mo
mOS	11 mo	5 mo

Kudo, Lancet Oncol 2017
Le, GI-ASCO 2016;

ONO-12 (Attraction): Phase 3 trial in patients with advanced G/EGJ ≥ 2 prior chemo regimen



OP: survie

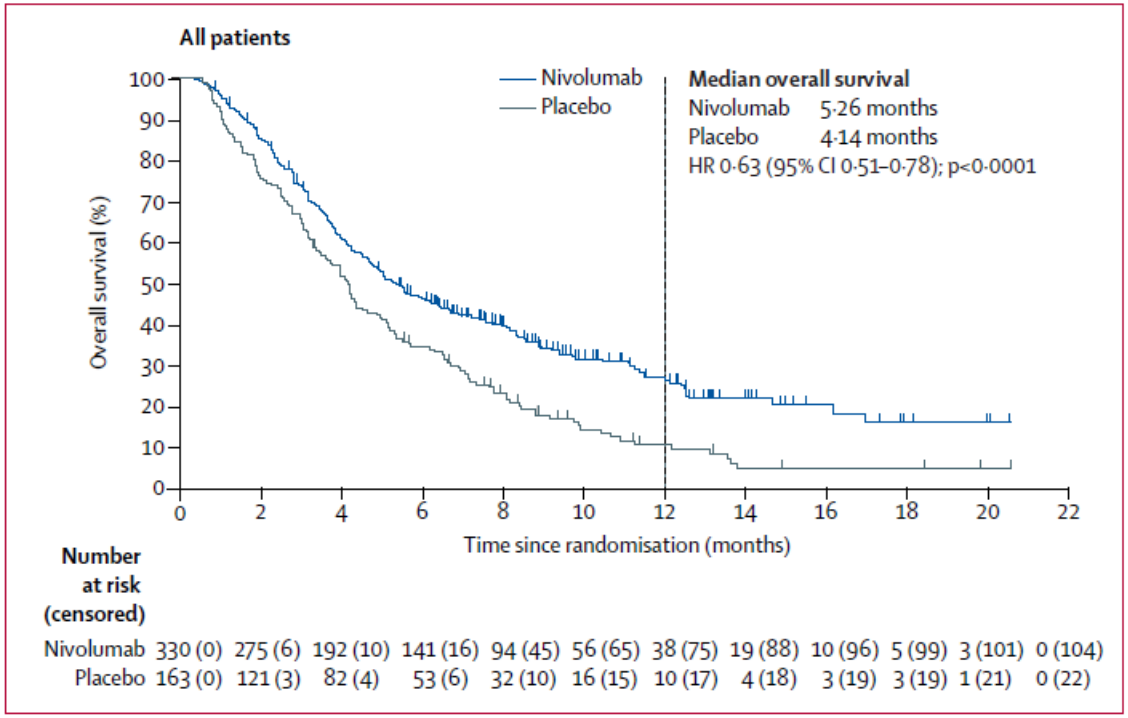
N= 330, PD-L1: all comers

ORR: 11,5%, mDOR: 9mo

Boku, ESMO 2017

ONO-12 (Attraction): survie

suivi médian: 15,7 m (12.1-27.2)



PD-L1 negatif	
Nivolumab (n=114)	**6.1** (4.8-8.6)
Placebo (n=52)	**4.2** (3.0-6.9)
Hazard ratio, **0.71** (95% CI, **0.50-1.01**)	

PD-L1 positif	
Nivolumab (n=16)	**5.2** (2.8-9.4)
Placebo (n=10)	**3.8** (0.8-5.0)
Hazard ratio, **0.58** (95% CI, **0.24-1.38**)	

Boku, ESMO 2017
Kang, Lancet Oncol 2017

ICM Institut régional du Cancer Montpellier

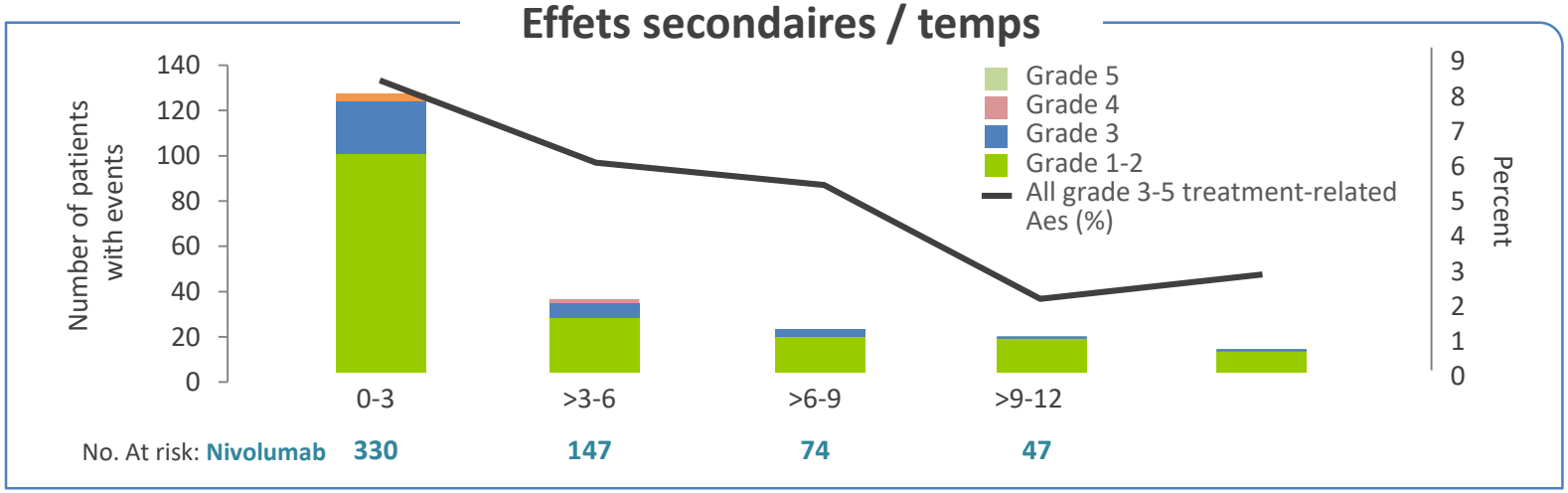
SIRIC MONTPELLIER CANCER Site de Recherche Intégrée sur le Cancer

Institut de Recherche en Cancérologie IRC Montpellier

ONO-12 (Attraction): toxicité

	Nivolumab		Placebo	
	Tout Grade (%)	Grade ¾ (%)	Tout Grade (%)	Grade ¾ (%)
Total	43	11	27	4
Prurit	9	0	6	0
Diarrhée	7	<1	2	0
Rash	6	0	3	0
Fatigue	5	<1	6	1
Anorexie	5	1	4	<1
Nausées	5	0	2	0
Hypothyroïdie	3	0	<1	0
Fièvre	3	<1	2	0

Effets secondaires / temps

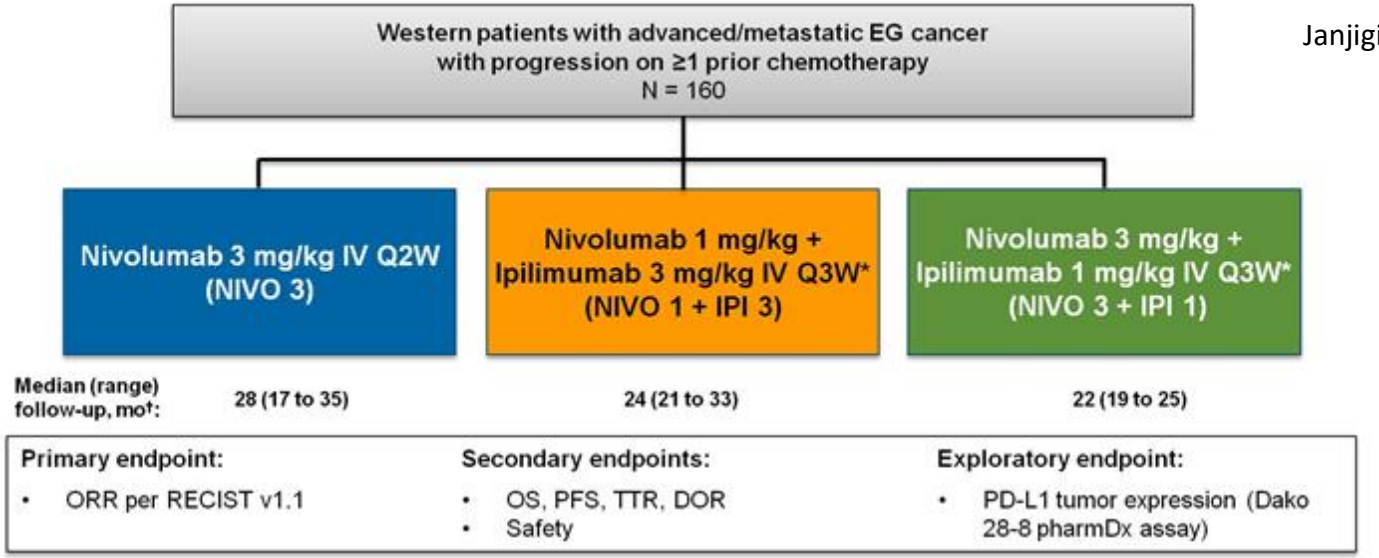


Boku, ESMO 2017

Checkmate 032 (update) – adeno OE/JOG/G N3q2w vs N3-IPI1q3w vs N1-IPI3q3w

- Nivo améliore la survie (vs Pbo) chez pts asiatiques avec K JOG/G prétraités par 2 lignes de CT
- N+IPI: association de référence ds mélanome
- 1ers résultats N+IPI ASCO 2016 chez pts occidentaux – ici **UPDATE**

Janjigian, ASCO 2017



Nivolumab + IPI (Checkmate 032)

Items	Nivo 3 mono	Nivo 1 – IPI 3	Nivo 3 – IPI 1
N	59	49	52
≥ 3 lignes antérieures de CT	49%	46%	38%
Severe TRAE	5%	35%	17%
ORR%	13.6 (6-25)	26.1 (14.3-41)	10.2 (3.4-22)
mDOR	7 mo	5.6 mo	na
mPFS	1.4 mo	1.5 mo	1.6 mo
mOS	5 mo	6.9 mo	4.8 mo
1yr-OS	36%	34%	na

Not a comparative study !

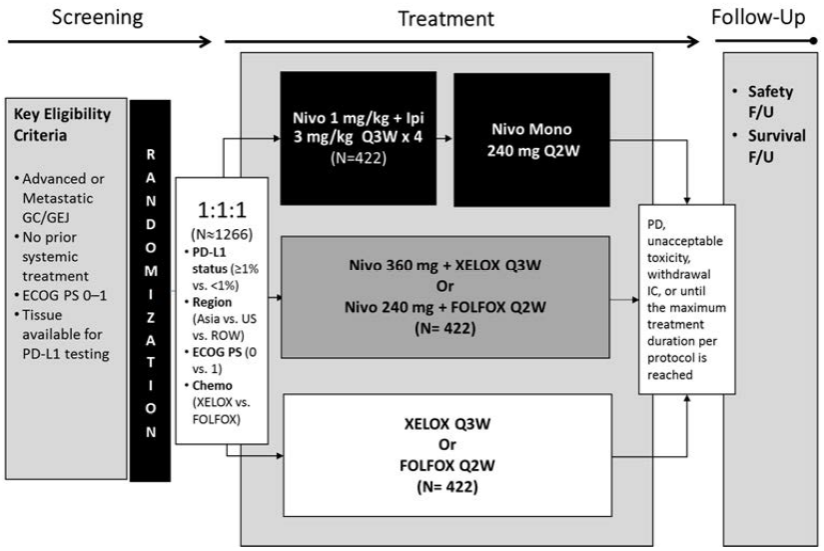
Janjigian, ASCO 2017

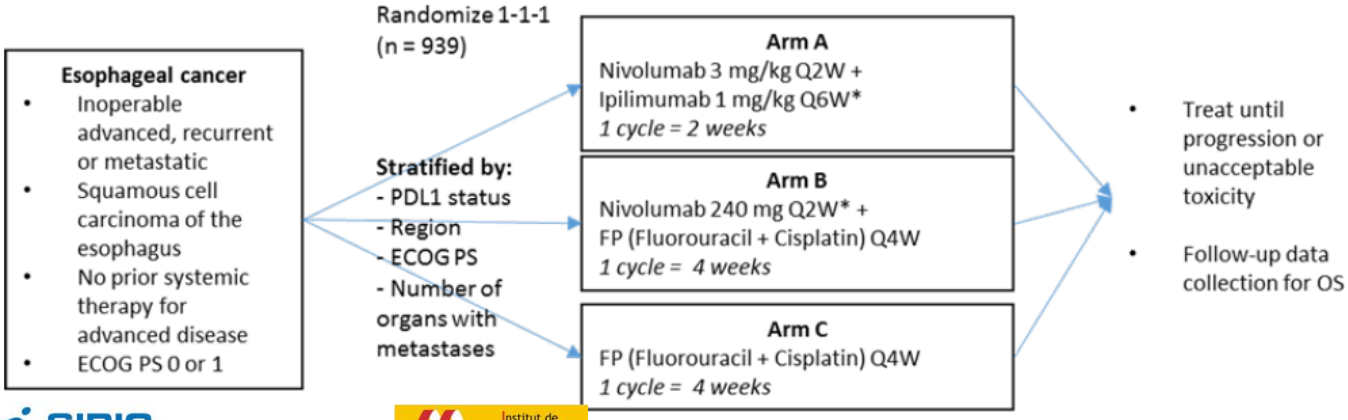
Nivolumab (± IPI)

- Nivo3
  - 1ère étude de phase III positive dans le cancer gastrique en L3.
  - Efficacité non restreinte au statut PD-L1
  - Bonne tolérance
  - Résultats à confirmer en occident

- Nivo1 – IPI 3 sélectionné pour développement futur:
  - ORR: 24% (40% chez les PD-L1+)
  - Survie: 28% à 18 mois (comme Nivo seul)
  - 40% sévère TRAE

BMS CA209-649 – L1 estomac
BMS CA209-648 – L1 œsophage (SCC)





ICM Institut régional du Cancer Montpellier

SIRIC MONTPELLIER CANCER Site de Recherche Intégrée sur le Cancer

Institut de Recherche en Cancérologie IRC Montpellier

Autres checkpoint inhibiteurs

Anti-CTLA4

Anti-PDL1

Anti-LAG3

Cancers localisés

BMS adjuvant/neoadjuvant

- ONO-4538: nivolumab+CT adjuvant (vs CT), gastric cancer.
- **CheckMate 577: CRT-chir puis nivolumab vs pbo, œsophage/JOG**
- CheckMate 906 (?): nivolumab vs N1IPI3 puis CRT-nivo puis chir

Keynote 585 – estomac/JOG périOp

- A Phase III, Randomized, Double-Blind, Clinical Trial of Pembrolizumab plus Chemotherapy (FLOT) versus Placebo plus Chemotherapy as Neoadjuvant/Adjuvant Treatment for Subjects with Gastric and Gastroesophageal Junction (GEJ) Adenocarcinoma

Predictive biomarkers for checkpoint inhibitor-based immunotherapy in E & EG cancer

ICM Institut régional du Cancer Montpellier
SIRIC MONTPELLIER CANCER Site de Recherche Intégrée sur le Cancer
Institut de Recherche en Cancérologie IRC Montpellier

MSI: un facteur très favorable de réponse et de survie

Keynote 059

Response by MSI Status (n = 174)

4.0% of patients were MSI-High

Response[a]	MSI-High (n = 7)		Non–MSI-High (n = 167)	
	%	95% CI	%	95% CI
ORR	57.1	18.4-90.1	9.0	5.1-14.4
CR	14.3	0.4-57.9	2.4	0.7-6.0
PR	42.9	9.9-81.6	6.6	3.3-11.5
DCR[b]	71.4	29.0-96.3	22.2	16.1-29.2

CheckMate 032

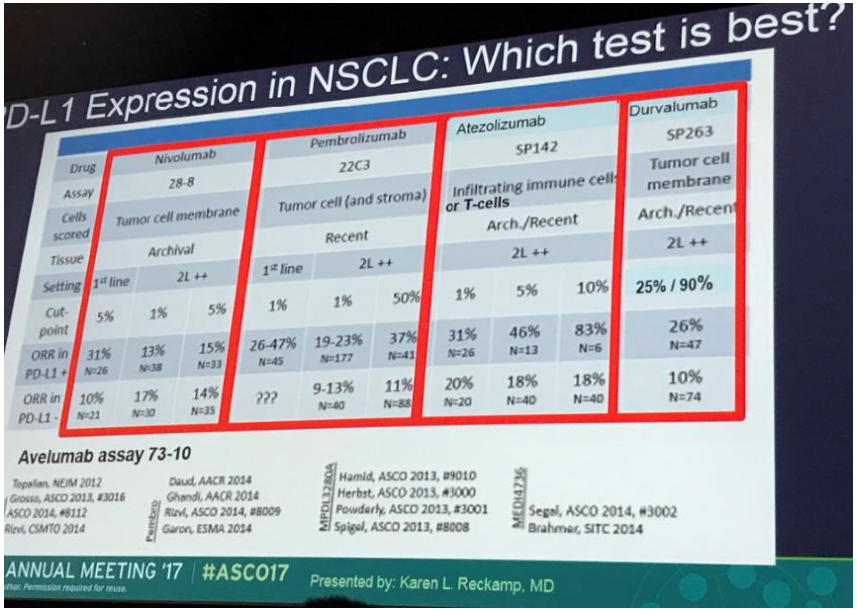
MSI-H: 11/160 pts ou plutôt 11/72 pts (15%)

Table 3. OS by MSI status

	NIVO 3 (n = 59)			NIVO 1 + IPI 3 (n = 49)			NIVO 3 + IPI 1 (n = 52)		
	MSI-H (n = 7)	Non–MSI-H (n = 18)	MSI-U (n = 34)	MSI-H (n = 2)	Non–MSI-H (n = 21)	MSI-U (n = 26)	MSI-H (n = 2)	Non–MSI-H (n = 22)	MSI-U (n = 28)
Median OS, months [95% CI]	15 [2, NE]	6 [3, 12]	5 [3, 16]	NR [1, NE]	9 [4, 23]	4 [2, 16]	NR [2, NE]	4 [3, 9]	5 [2, 9]
OS rate, % [95% CI]									
12 months	57 [17, 84]	33 [14, 55]	39 [22, 56]	50 [1, 91]	36 [16, 56]	33 [16, 51]	50 [1, 91]	23 [8, 43]	23 [9, 40]
18 months	29 [4, 61]	17 [4, 37]	31 [15, 48]	50 [1, 91]	30 [12, 51]	24 [9, 42]	50 [1, 91)]	6 [0, 23]	15 [5, 31]

Les tumeurs MSI sont quasiment toutes PDL1+

PDL1: un marqueur perfectible à standardiser



- The analysis of PD-L1 expression within tumors is not standardized.
- Different staining techniques are available, using different Abs for and different levels of positivity.
- Some studies looked at PD-L1 expression by tumor cells, whereas others also included its expression by cells of the microenvironment.
- PD-L1 expression is dynamic, i.e: inducible, notably by IFN-γ exposure. Therefore, a tumor which does not express PD-L1 at baseline may become PD-L1-positive in an inflammatory background (CTLA4 inhib treatment, radiation therapy, etc…).
- Lastly, a significant percentage of patients negative for PD-L1 respond to anti-PD-1/PD-L1 therapy.

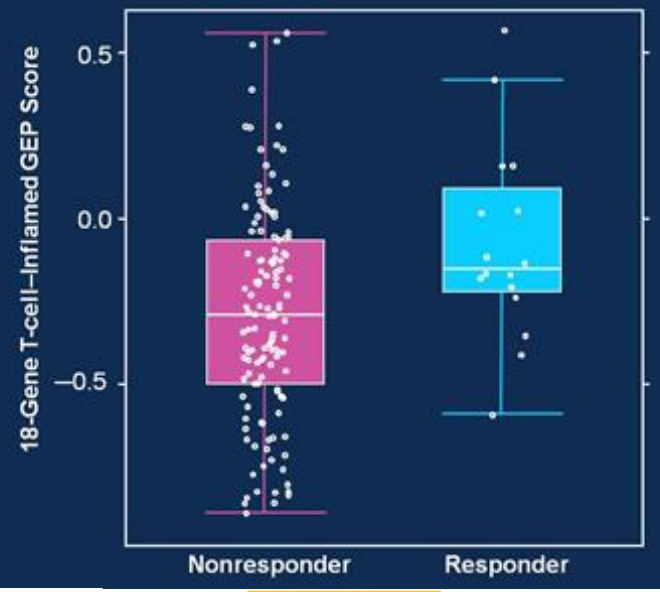
Gene Expression Signature

- 18 gene T-cell inflamed GEP predictive of response to pembrolizumab[1-3]
  - Derived by testing, validation, and refinement of immune-related gene sets across a variety of tumor types[1-3]
- GEP score is a weighted sum of normalized values for the genes[a]

18 genes

CCL5, CD27, CD274 (PD-L1), CD276 (B7-H3), CD8A, CMKLR1, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NKG7, PDCD1LG2 (PD-L2), PSMB10, STAT1, TIGIT

T-cell–Inflamed GEP Score by Response (n = 144)



T-cell–inflamed GEP score significantly associated ($P = 0.014$) with improved response to pembrolizumab

Fuchs, ASCO 2017

Predictive biomarkers for checkpoint inhibitor-based immunotherapy **in E & EG cancer**

- Microsatellite instability (…as the results of Mismatch-repair deficiency)- 4-22%
- PD-L1 expression (including EBV-mediated GC – 9% of GC – with PD-L1/L2 amplif)
- Immune-gene signature (…association with response to pembro)
- Mutational (or neoantigen) burden
- **Mononuclear inflammatory density score (association with response to Pbro)**
- **TILs**
- **T-cell receptor clonality**
- **Multiplex (multispectral) immunochemistry**
- **Microbiota?**

Falchetti, Hum Pathol 2008; Oki, Ann Surg Oncol 2009; Derks, OncoTargets2015
Ribas, ASCO 2015; Shankaran, ASCO 2015; Muro, Lancet Oncol 2016; Fuchs, ASCO 2017;
The Cancer Genome Atlas Research Network, Nature 2014; Le, N Engl J Med 2015

Conclusion

- PD1 inh (+/- CTLA4 inh) and PD-L1 inh, as well as PD1 inh combined to standard chemo, demonstrate encouraging efficacy (and manageable safety), irrespective of tumor PD-L1 expression
- In need of biomarker development for patient selection and prognostication