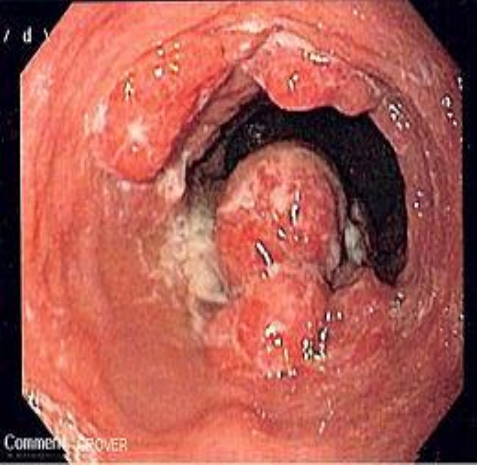
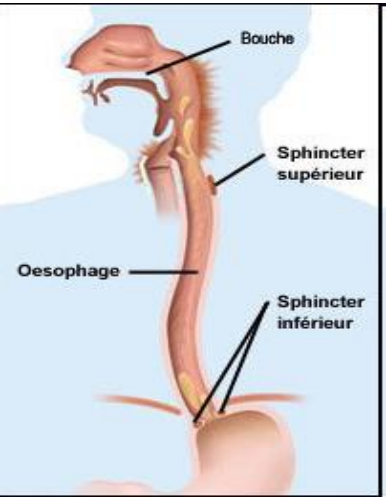
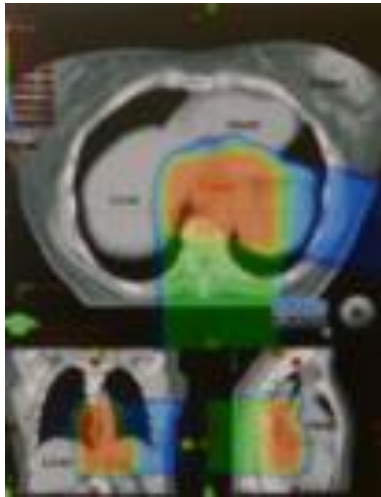


Cancer de la Jog et de l'estomac des thérapies ciblées à l'immunothérapie ?



Dr JP METGES
Institut de Cancérologie et d'Hématologie
Inserm 1078
Pole régional Brest-Rennes
CHU MORVAN
BREST

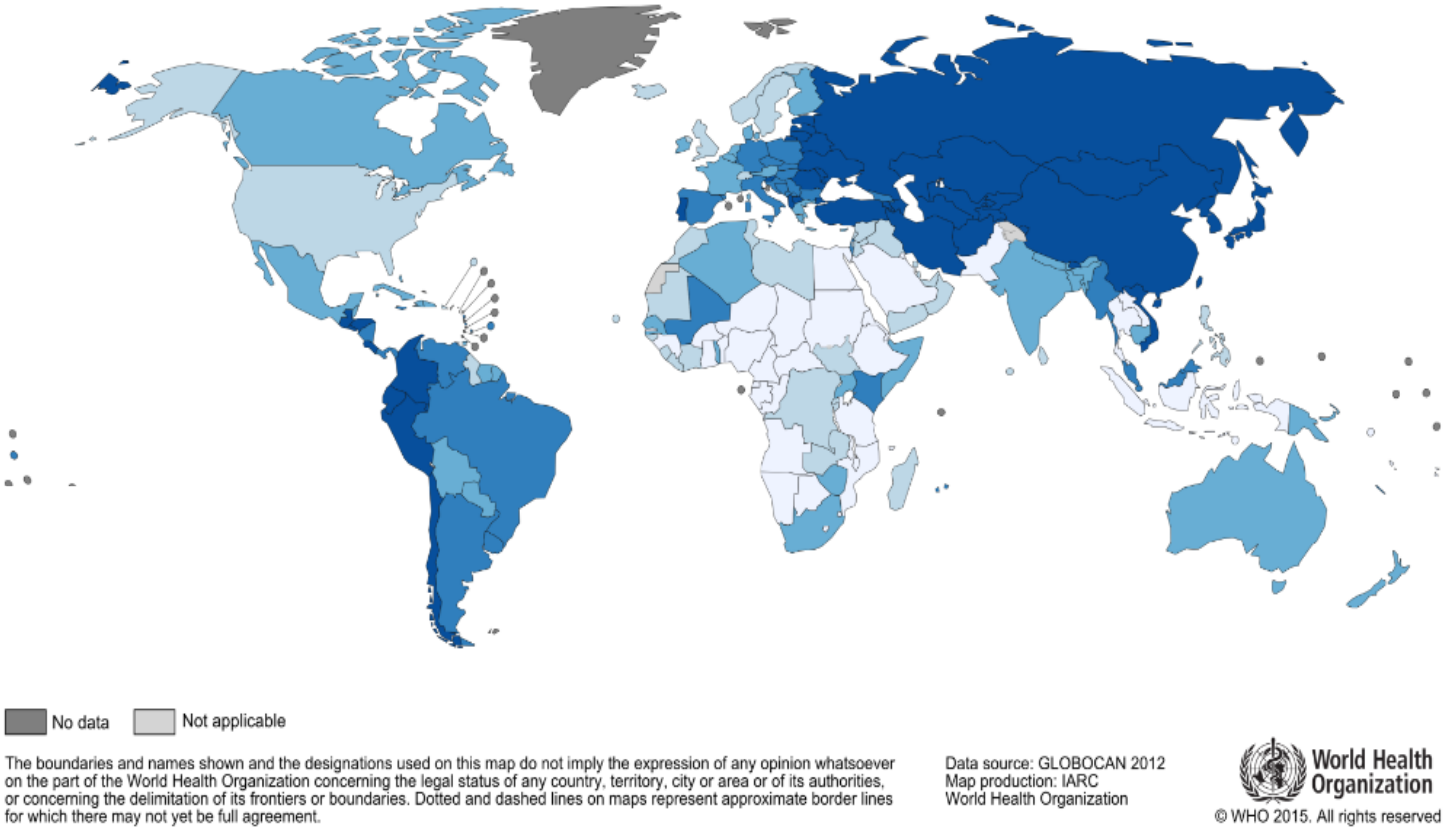


Epidémiologie des cancers gastriques

3ème cause de décès par cancer dans le monde

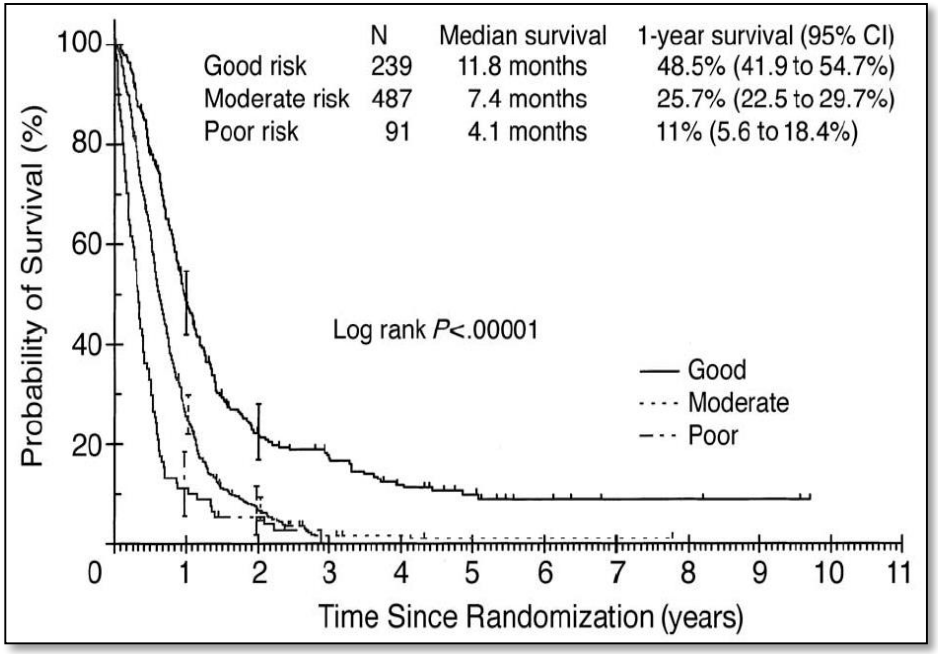
Données WHO 2012

Incidence: 952 000 cas/an
Mortalité: 723 M décès/an



http://globocan.iarc.fr/old/FactSheets/cancers/stomach-new.asp#TOP

Palliative CT : a real option ?



1080 patients (1992-2001)

↓

Four Prognostic Factors

- ECOG 2-3
- Liver metastasis
- Peritoneal carcinomatosis
- PAs ≥ 100 UI

Score	Survie (mois)
0	11,8
1 – 2	7,4
3 - 4	4,1

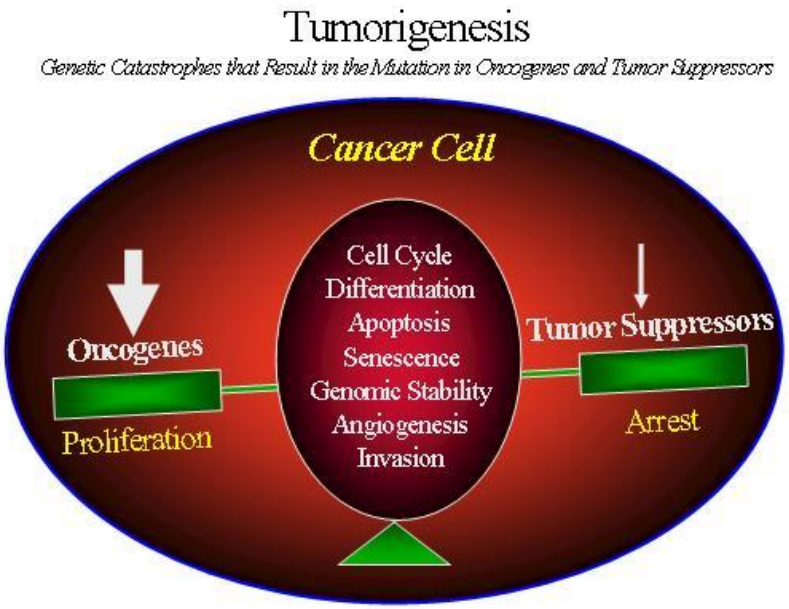
Chau et al. J Clin Oncol 2004

FIRST LINE : Several options !!!

	EOX or EOF[1]	ECX or EOX[1]	DCF[2]	ECF[3]	XP[4]	FLO[5]	FOLFIRI[6]	mDCF[7]	TFOX[8] (TEF)
N	489	513	221	126	160	112	209	54	55
ORR (%)	44	45	37	45	46	35	39	49	46.6
SSP (months)	6.7	6.5	5.6	7.4	5.6	5.8	5.3	9.7	7.6
OS (months)	10.4	10.9	9.2	8.9	10.5	10.7	9.5	18.8	14.6

1. Cunningham D, et al. N Engl J Med. 2008;358:36-46. 2. Van Cutsem E, et al. J Clin Oncol. 2006;24:4991-4997. 3. Webb A, et al. J Clin Oncol. 1997;15:261-267.4. Kang YK, et al. Ann Oncol. 2009;20:666-673. 5. Al-Batran SE, et al. J Clin Oncol. 2008;26:1435-1442. 6. Guimbaud R, et al. J Clin Oncol. 2014;32:3520-3526. 7. Shah et al. J Clin Oncol 2015. 8. Van Cutsem et al. ICO 2015

Decision in ONCOLOGY

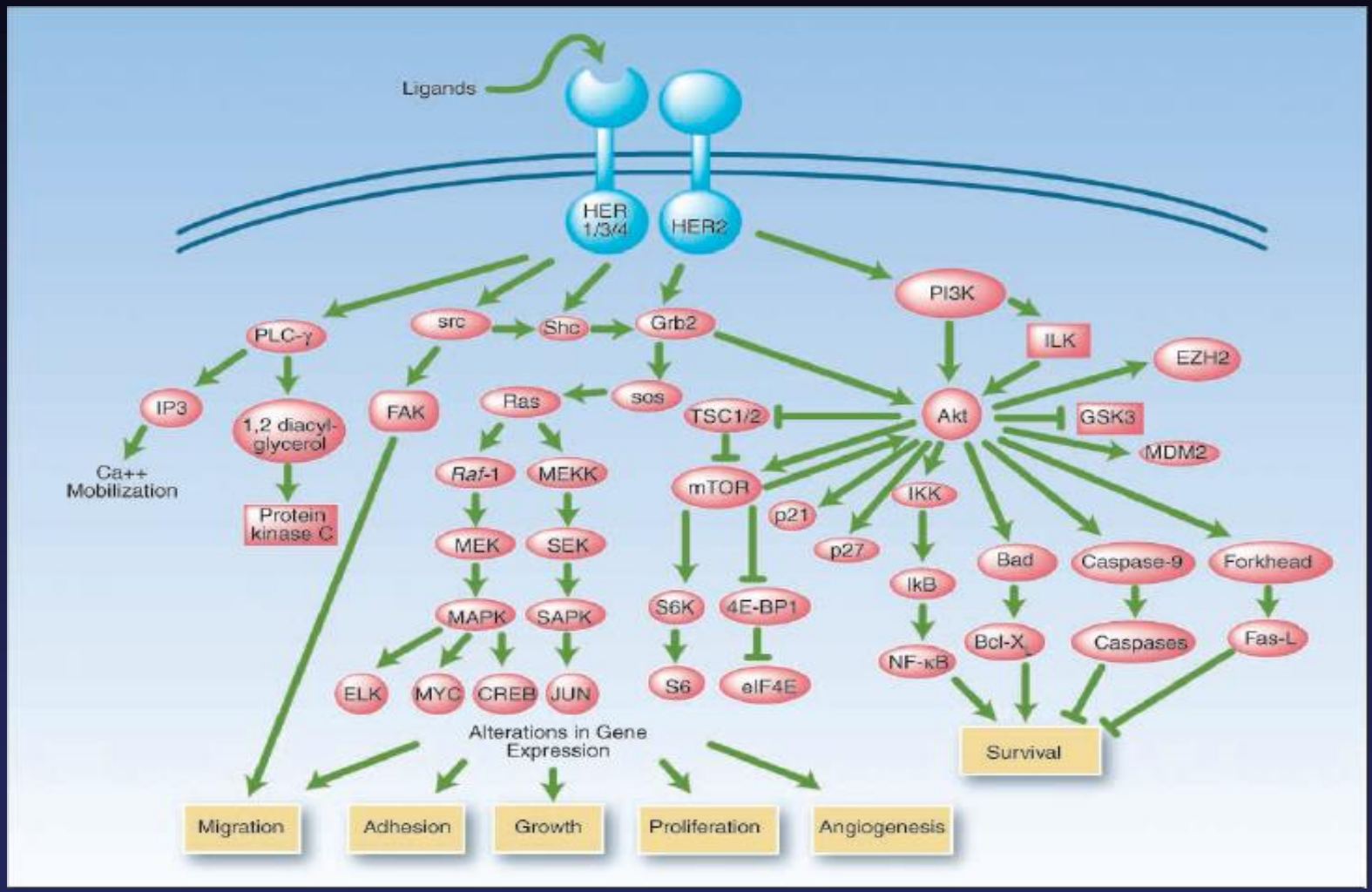


WHICH TARGET ?

WHICH OPTIONS ?


HERE
THERE

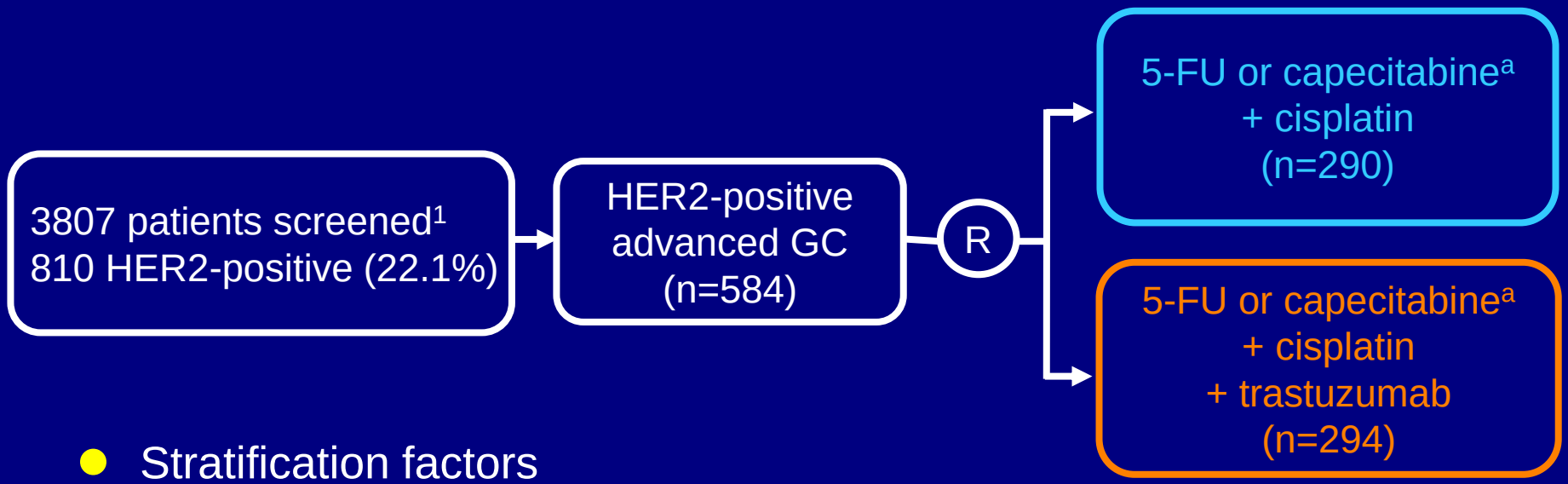
Targeting the HER2



Meric-Bernstam et al, 2006; Olayioye et al, 2000; Rowinski, 2003.

ToGA trial design

Phase III, randomized, open-label, international, multicenter study



- Stratification factors
  - advanced vs metastatic
  - GC vs GEJ
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU

[a]Chosen at investigator's discretion
GEJ, gastroesophageal junction

[1]Bang et al; Abstract 4556, ASCO 2009

Treatment regimens

- **Capecitabine**
  1000 mg/m^2 bid d1-14 q3w x 6
- **5-fluorouracil**
  800 mg/m^2/day continuous iv infusion d1-5 q3w x 6
- **Cisplatin**
  80 mg/m^2 q3w x 6
- **Trastuzumab**
  8 mg/kg loading dose followed by 6 mg/kg q3w until PD

ToGA trial end points

- Primary end point:
  - overall survival
- Secondary end points
  - PFS, TTP, ORR, Clinical Benefit Rate, Duration of Response, QoL, safety, pain intensity, analgesic consumption, weight change, pharmacokinetics
- Sample size assumptions
  - median OS improvement from 10 to 13 months (HR 0.77)
  - α-level = 0.05, 80% power
  - required sample size: 584 patients randomized 1:1
- Analyses
  - 1st pre-planned interim analysis after 230 events (50%)
  - 2nd interim analysis after 345 events (75%) considered final by Independent Data Monitoring Committee

Main patient selection criteria

Inclusion criteria

- Adenocarcinoma of stomach or GEJ
- Inoperable locally advanced and/or metastatic disease
- Measurable disease (RECIST), or non-measurable evaluable disease
- HER2-positive tumor (centrally assessed)
  - IHC 3+ and/or FISH+
- Adequate organ function and ECOG performance status ≤2
- Written informed consent

Exclusion criteria

- Previous adjuvant chemotherapy within 6 months
- Chemotherapy for advanced disease
- Congestive heart failure or baseline LVEF <50%
- Creatinine clearance <60 mL/min

IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; LVEF, left ventricular ejection fraction

Patient demographics and baseline characteristics

Characteristic	F+C n=290	F+C + trastuzumab n=294
Sex, %		
Male / Female	75 / 25	77 / 23
Age, median (range) years	59.0 (21-82)	61.0 (23-83)
Weight, median (range) kg	60.3 (28-105)	61.5 (35-110)
Region, n (%)		
Asia	166 (56)	158 (53)
C/S America	26 (9)	27 (9)
Europe	95 (32)	99 (33)
Other	9 (3)	14 (5)
Type of GC (central assessment)		
Intestinal	74.2[a]	76.8[b]
Diffuse	8.7[a]	8.9[b]
Mixed	17.1[a]	14.3[b]
Prior gastrectomy	21.4	24.1

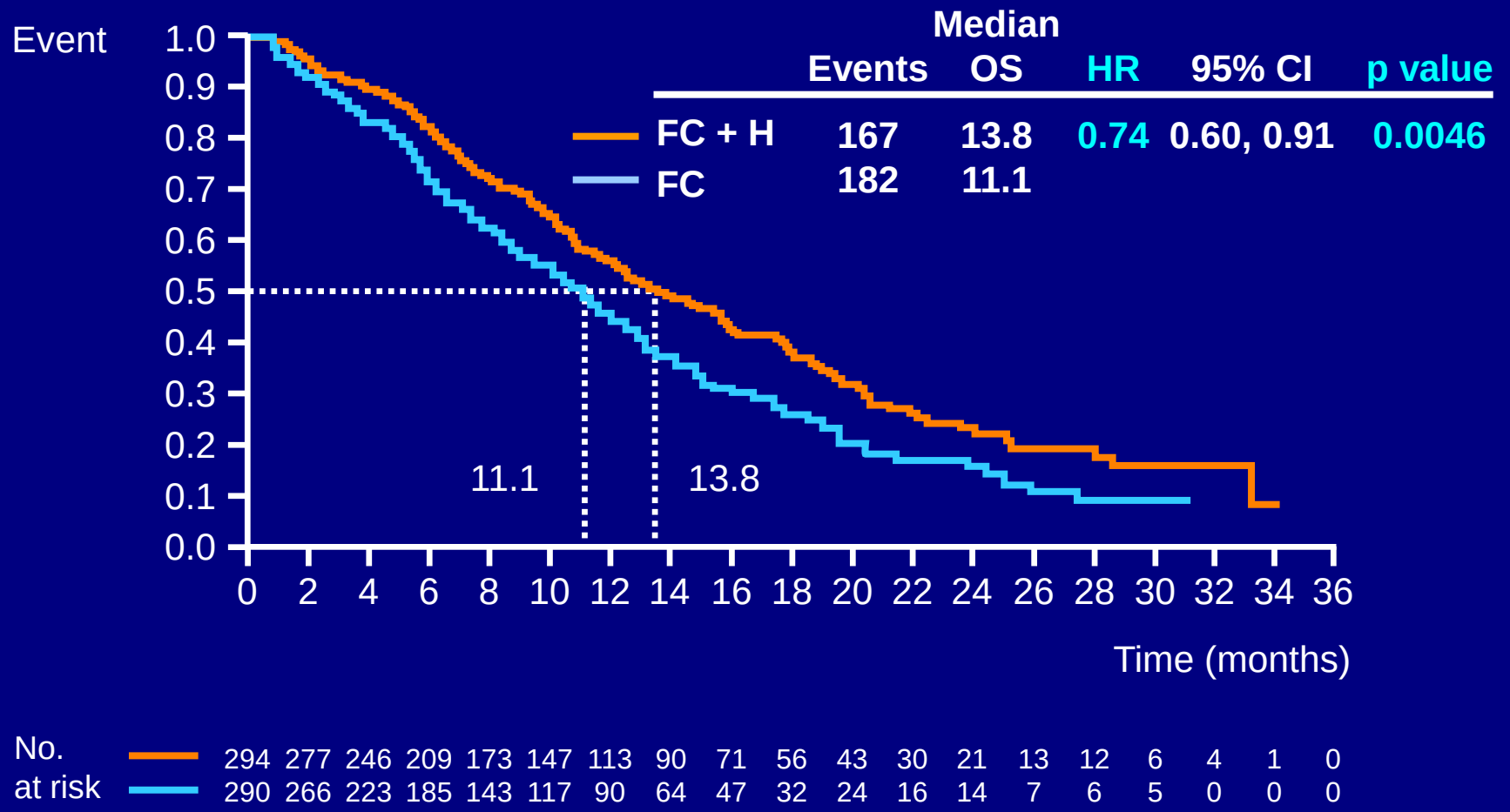
Highest recruitment was from Korea, Japan, China and Russia

F, fluoropyrimidine; C, cisplatin [a]n=287; [b]n=293

Stratification factors

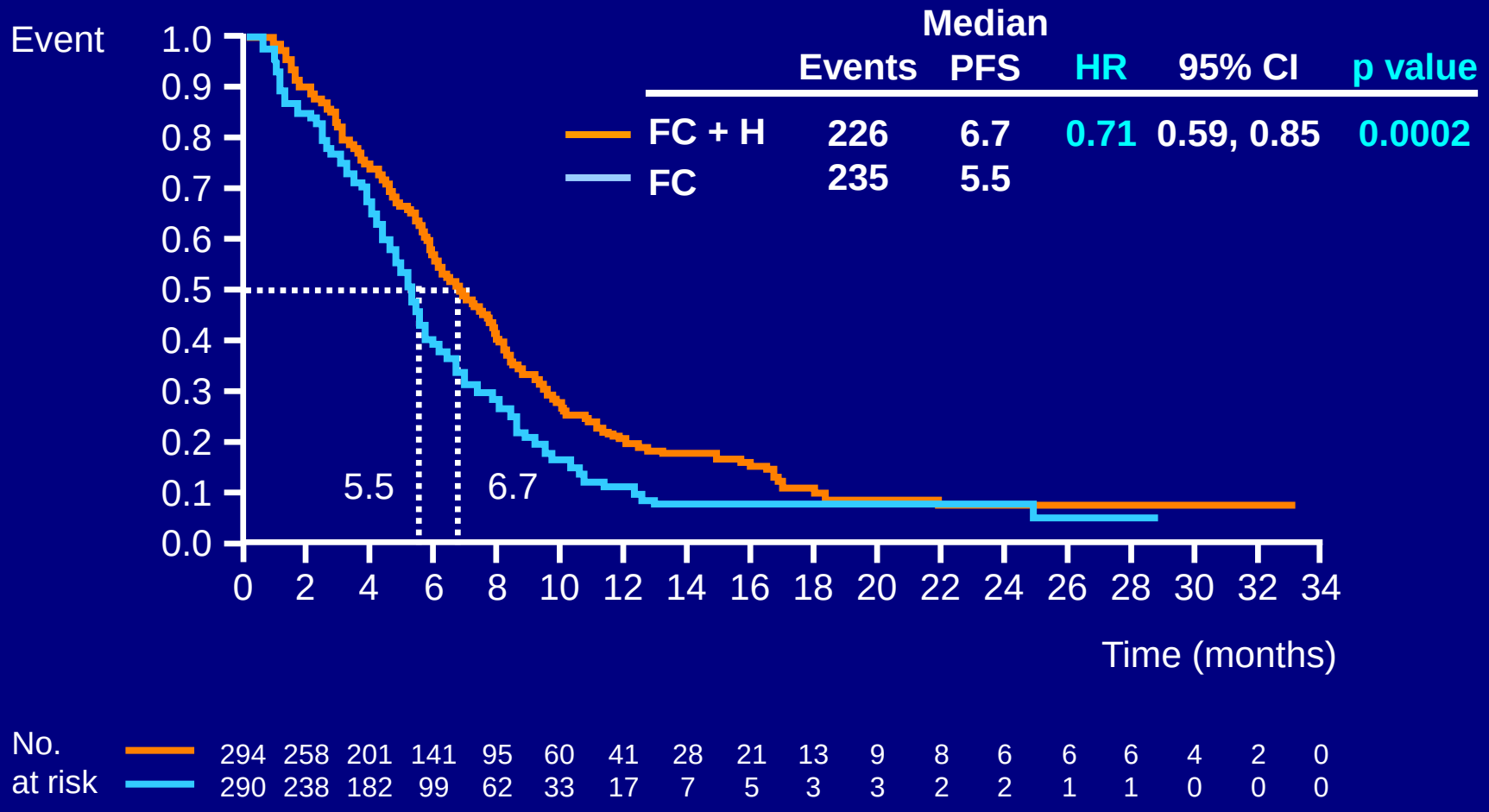
Characteristic, %	F+C n=290	F+C + trastuzumab n=294
Metastatic disease	96.6	96.6
Measurable disease	88.6	91.5
Primary site		
Stomach	83.4	80.3
GE junction	16.6	19.7
ECOG PS		
0	36.2	34.4
1	54.5	55.4
2	9.3	10.2
Fluoropyrimidine		
Capecitabine	87.9	87.1
5-FU	12.1	12.9

Primary end point: OS

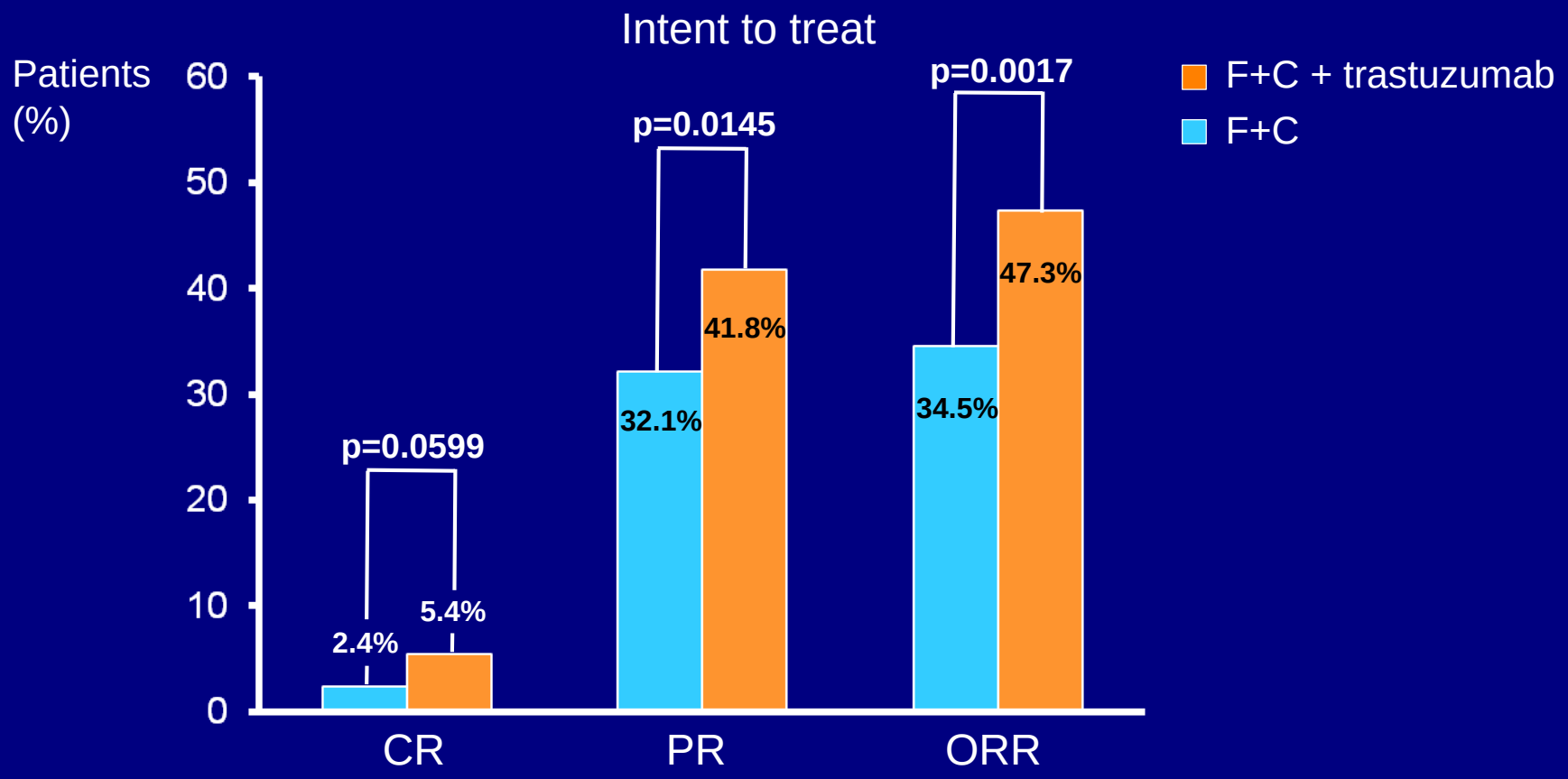


CI, confidence interval; H, trastuzumab

Secondary end point: PFS



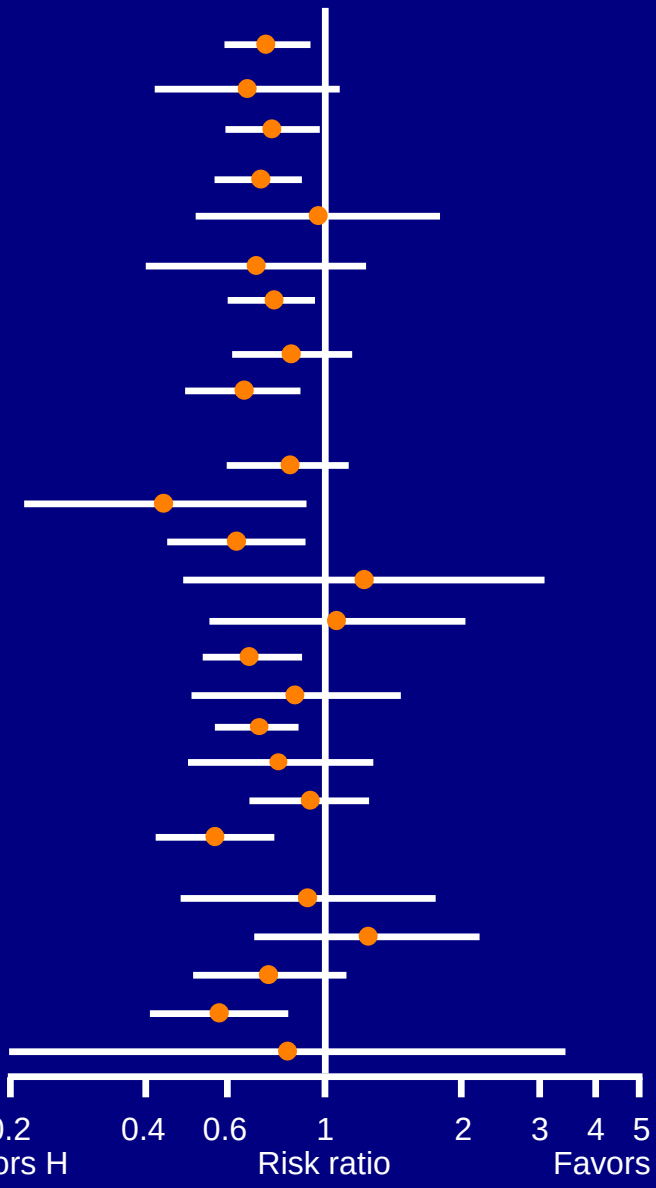
Secondary end point: tumor response rate



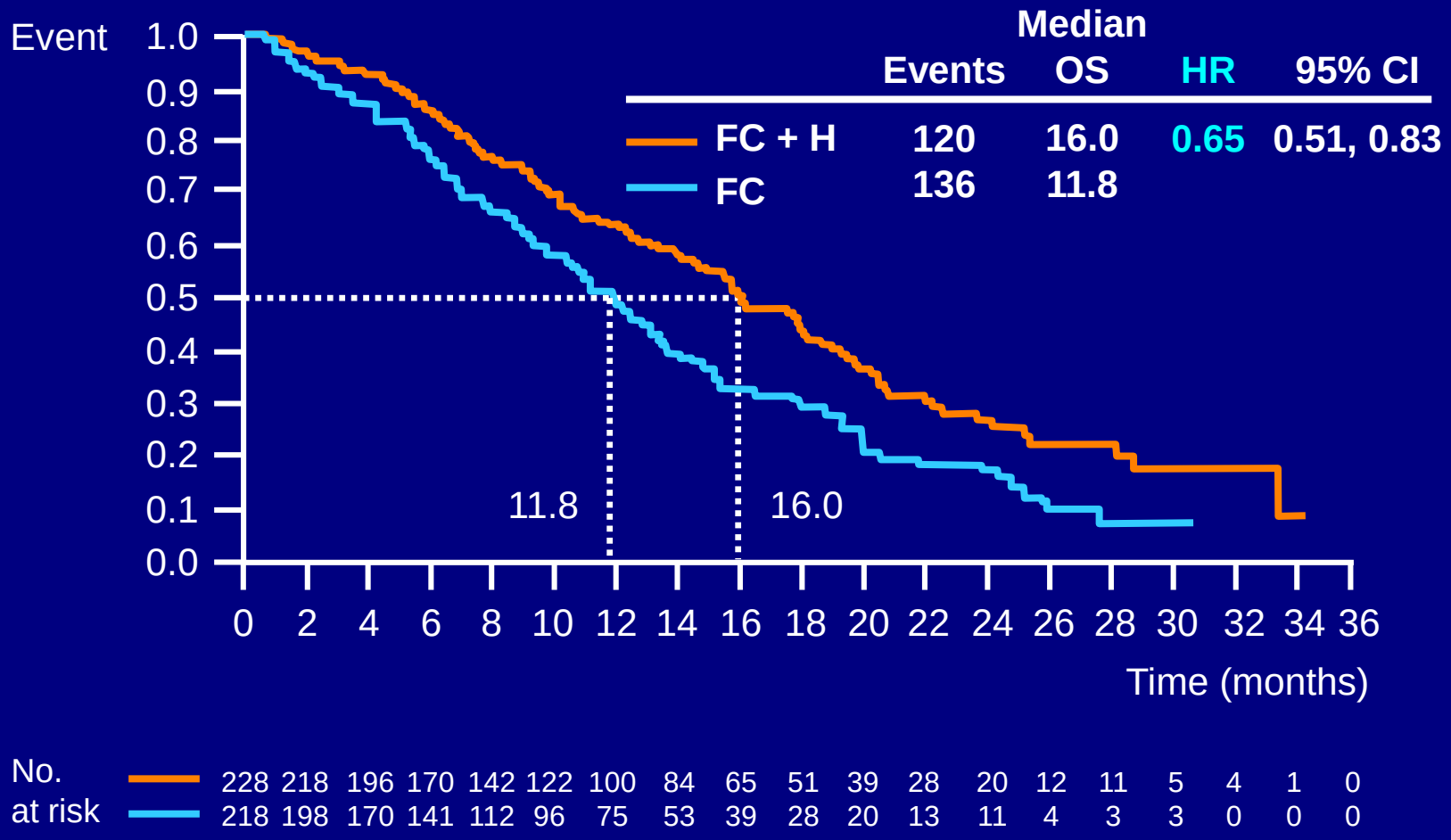
ORR= CR + PR
CR, complete response; PR, partial response

Efficacy: OS subgroup analysis

Category	Subgroup	N	HR	95% CI
All	All	584	0.74	0.60, 0.91
Primary site	GEJ	106	0.67	0.42, 1.08
	Stomach	478	0.76	0.60, 0.96
ECOG PS	0-1	527	0.71	0.56, 0.89
	2	57	0.96	0.51, 1.79
Fluoropyrimidine	5-FU	73	0.70	0.40, 1.23
	Capecitabine	511	0.75	0.60, 0.95
Age group	<60	279	0.84	0.62, 1.14
	≥60	305	0.66	0.49, 0.88
Region	Asia	319	0.82	0.61, 1.11
	C/S America	52	0.44	0.21, 0.90
	Europe	190	0.63	0.44, 0.89
	Other	23	1.22	0.48, 3.08
GC type	Diffuse	51	1.07	0.56, 2.05
	Intestinal	438	0.69	0.54, 0.88
	Mixed	91	0.86	0.51, 1.46
Prior gastrectomy	No	451	0.72	0.57, 0.91
	Yes	133	0.81	0.49, 1.34
No. metastatic sites	1-2	298	0.93	0.68, 1.26
	>2	285	0.57	0.43, 0.77
HER2 result[a]	IHC 0/FISH+	61	0.92	0.48, 1.76
	IHC 1+/FISH+	70	1.24	0.70, 2.20
	IHC 2+/FISH+	159	0.75	0.51, 1.11
	IHC 3+/FISH+	256	0.58	0.41, 0.81
	IHC 3+/FISH-	15	0.83	0.20, 3.38



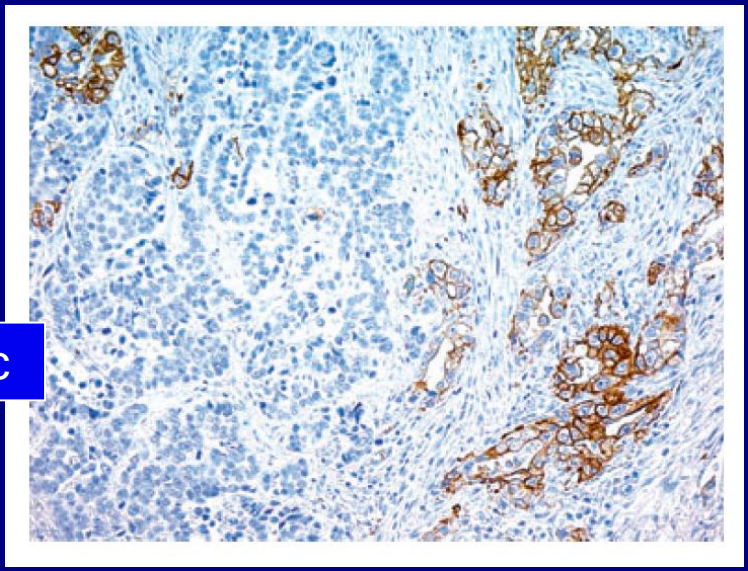
OS in IHC2+/FISH+ or IHC3+
(exploratory analysis)



Conclusions

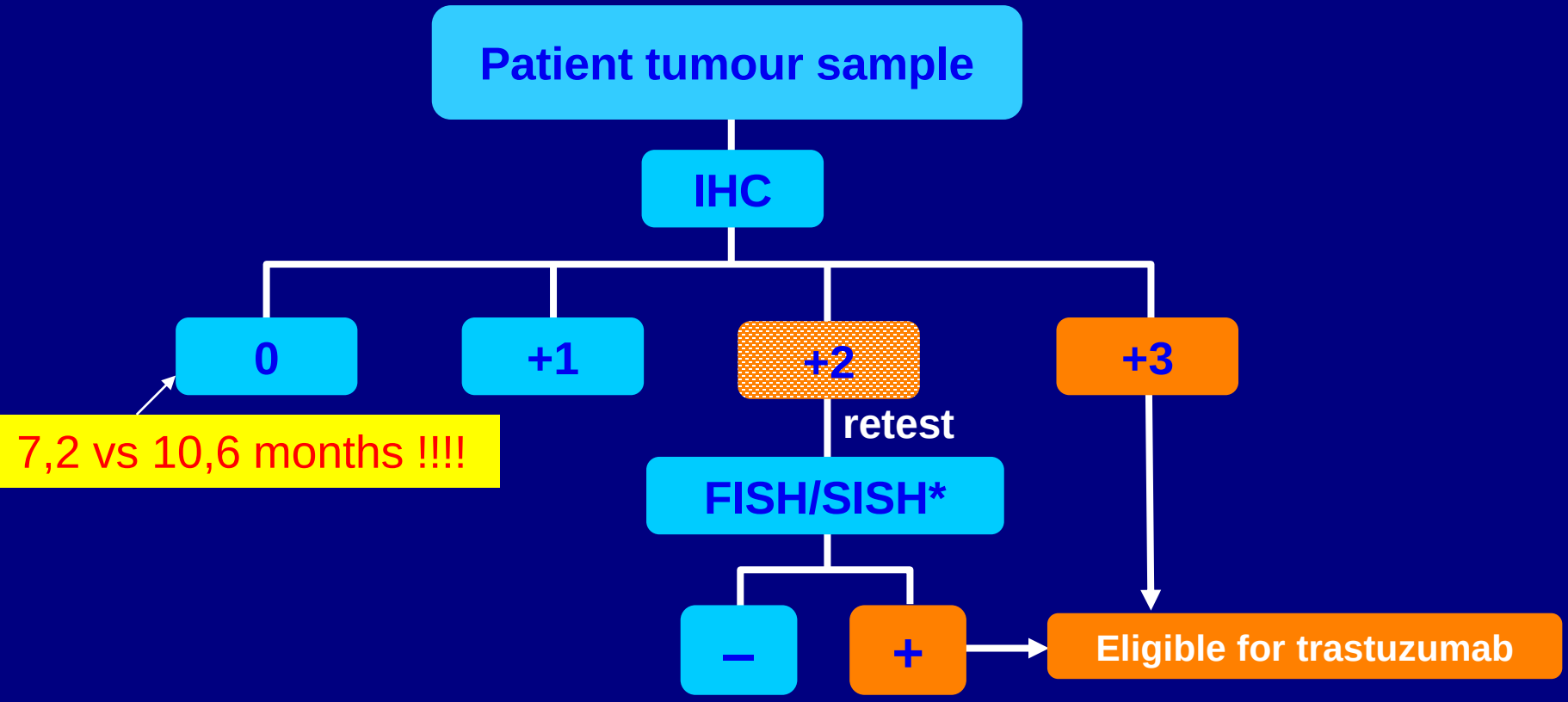
- Trastuzumab is the first biological to show a survival benefit in gastric cancer
- Trastuzumab in combination with chemotherapy is a new treatment option for patients with HER2-positive gastric adenocarcinoma

Gastric



Be carefull
IT IS NOT EASY
GUIDELINES !!!!!!

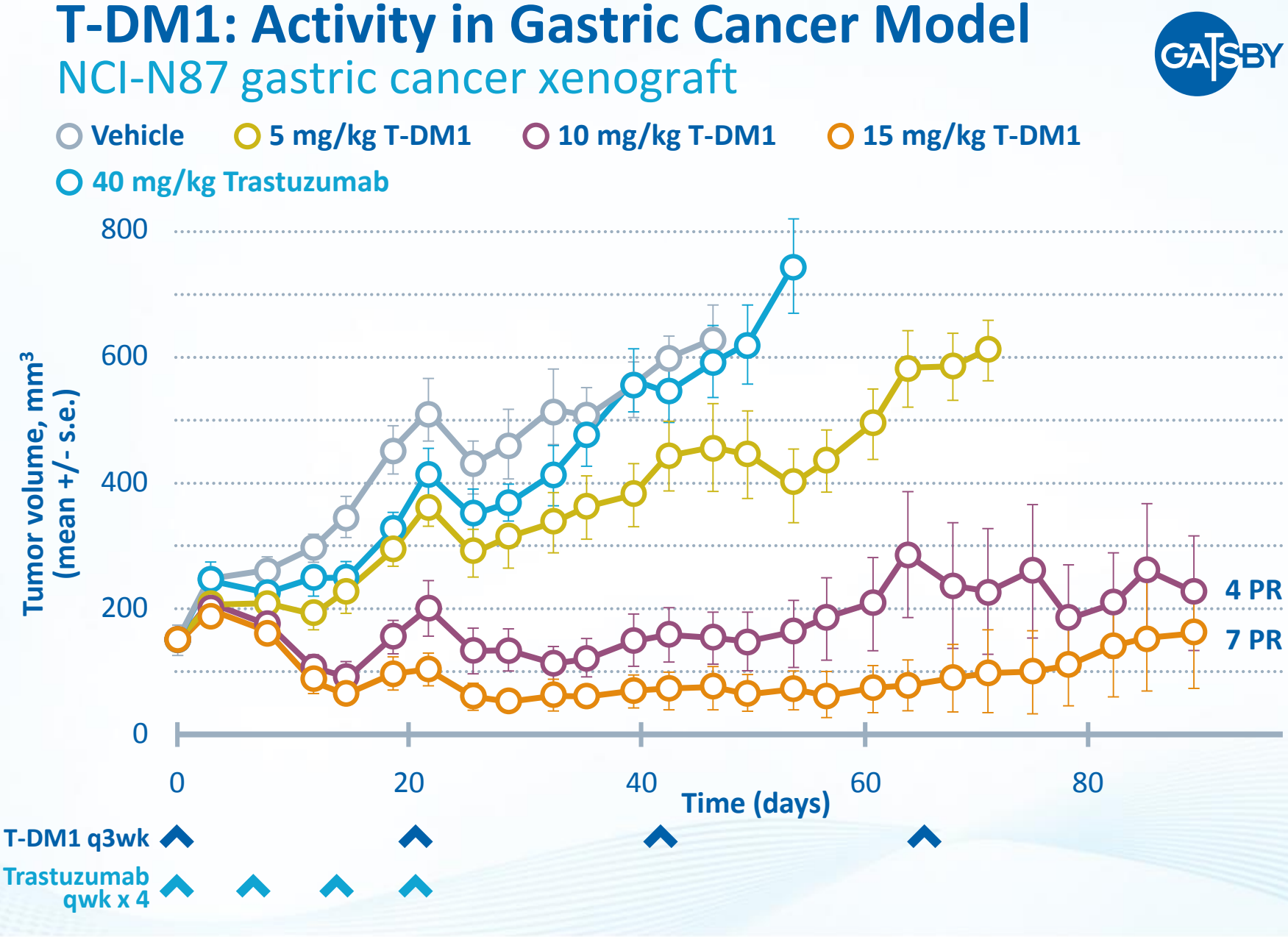
Suggested HER2 testing algorithm in GC/GEJ cancer



*cut off for FISH, SISH = HER2:CEP17 ratio ≥2

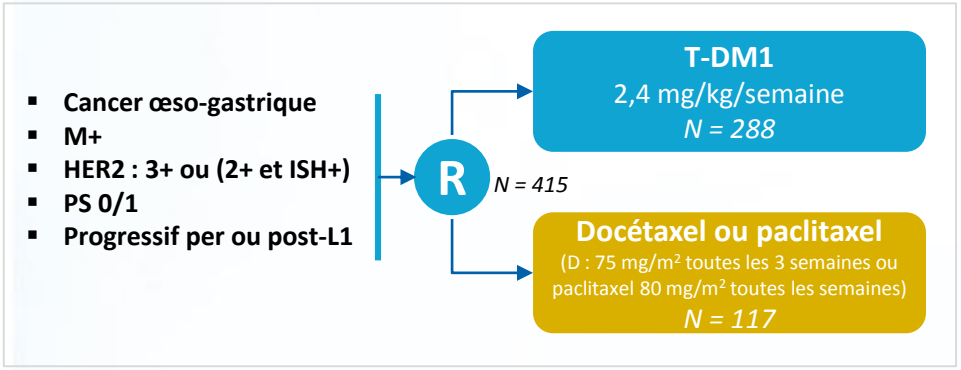
T-DM1: Activity in Gastric Cancer Model

NCI-N87 gastric cancer xenograft



Sein *vs* estomac : une autre histoire

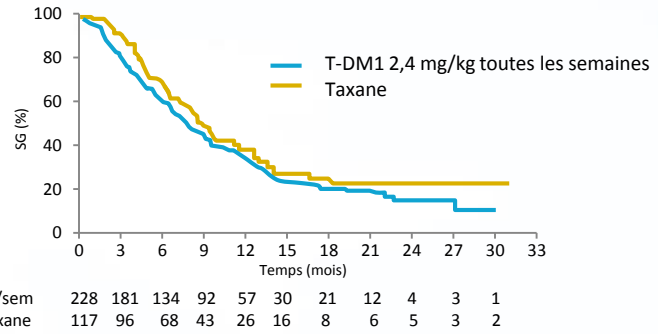
- L'étude TOGA avait à l'époque révolutionné la prise en charge du cancer de l'estomac en L1 métastatique faisant du résultat du statut HER2 (+ vs -) le préalable à la mise en traitement pour tous (étude TOGA).
- Sur l'exemple du sein métastatique (où ils sont tous les 2 indiqués), le TDM1 et le pertuzumab ont été investigués pour étudier leur impact dans le cancer de l'estomac.
- Les routes ont divergées une première fois avec la phase III négative GATSBY comparant TDM1 *versus* CT en L2 des cancers HER2 positifs.



N = 70, bras TDM-1 3,6 mg/kg/3 semaines : analysés à part

Objectif principal : Survie Globale

GATSBY : Résultats (survie globale)

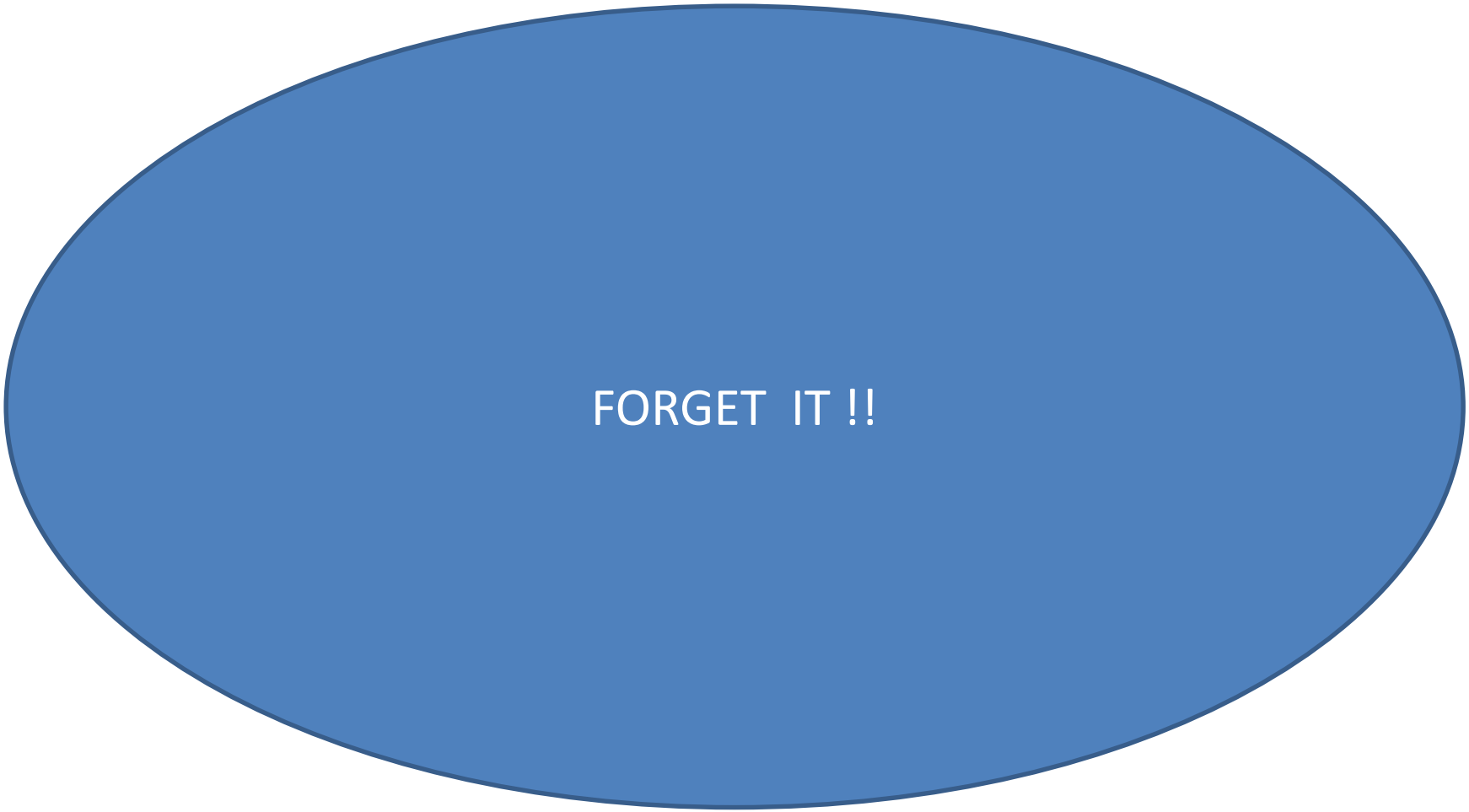


	TAXANE (N = 117)	T-DMI 2,4 mg/kg (N = 288)
Survie Globale (mois)	8,6	7,9
Evénements, n (%)	71 (60,7)	164 (71,9)
HR non stratifié (IC 95 %) T-DM1 hebdomadaire *vs* taxane	1,15 (0,87 – 1,51) ; p = 0,8589	

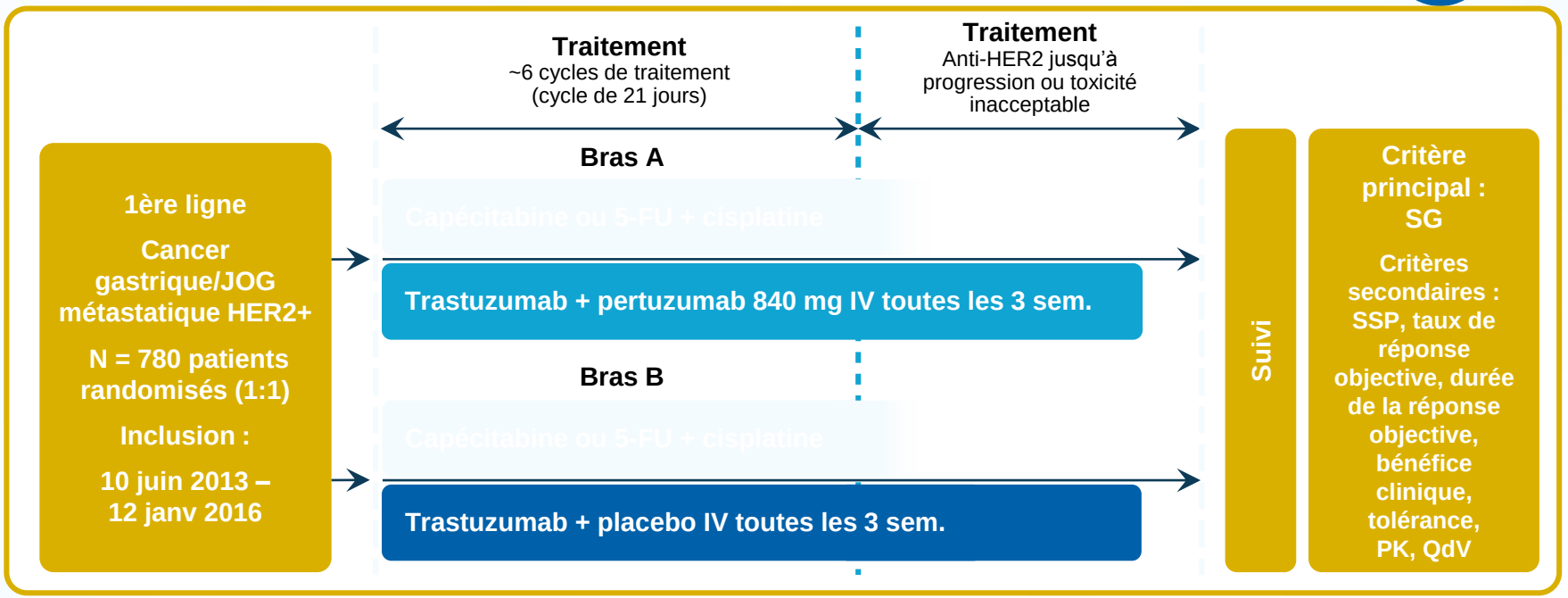
Kang *et al.* ASCO GI 2016, Abs 5

➢ Absence d'indication du TDM1 dans la prise en charge du cancer de l'estomac HER2+.

TDM1 in gastric cancer



JACOB : Méthodologie

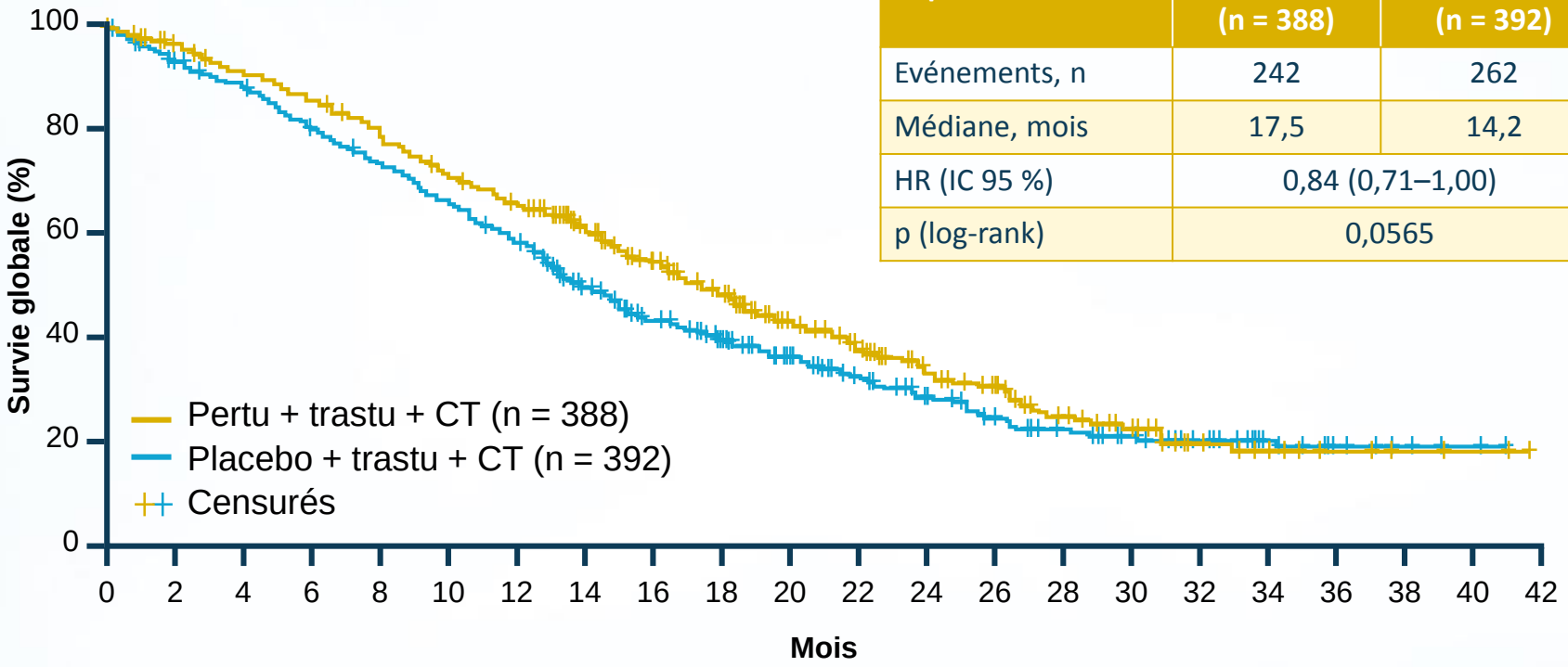


- **Critères d'éligibilité**
  - Cancer gastrique/JOG méta HER2+
  - IHC 3+, IHC 2+ et HIS-positif (testing centralisé)
  - ECOG PS 0 ou 1

- **Facteurs de stratification**
  - Région géographique (Asie [hors Japon], Japan, Am. du Nord/ Europe de l'Ouest/Australie, Am. du Sud/Europe de l'Est)
  - Gastrectomie antérieure (oui/non)
  - HER2 IHC 3+ vs IHC 2+/HIS-positif

Objectif principal : Survie Globale

Population ITT	Pertu + trastu + CT (n = 388)	Placebo + trastu + CT (n = 392)
Evénements, n	242	262
Médiane, mois	17,5	14,2
HR (IC 95 %)	0,84 (0,71–1,00)	
p (log-rank)	0,0565	

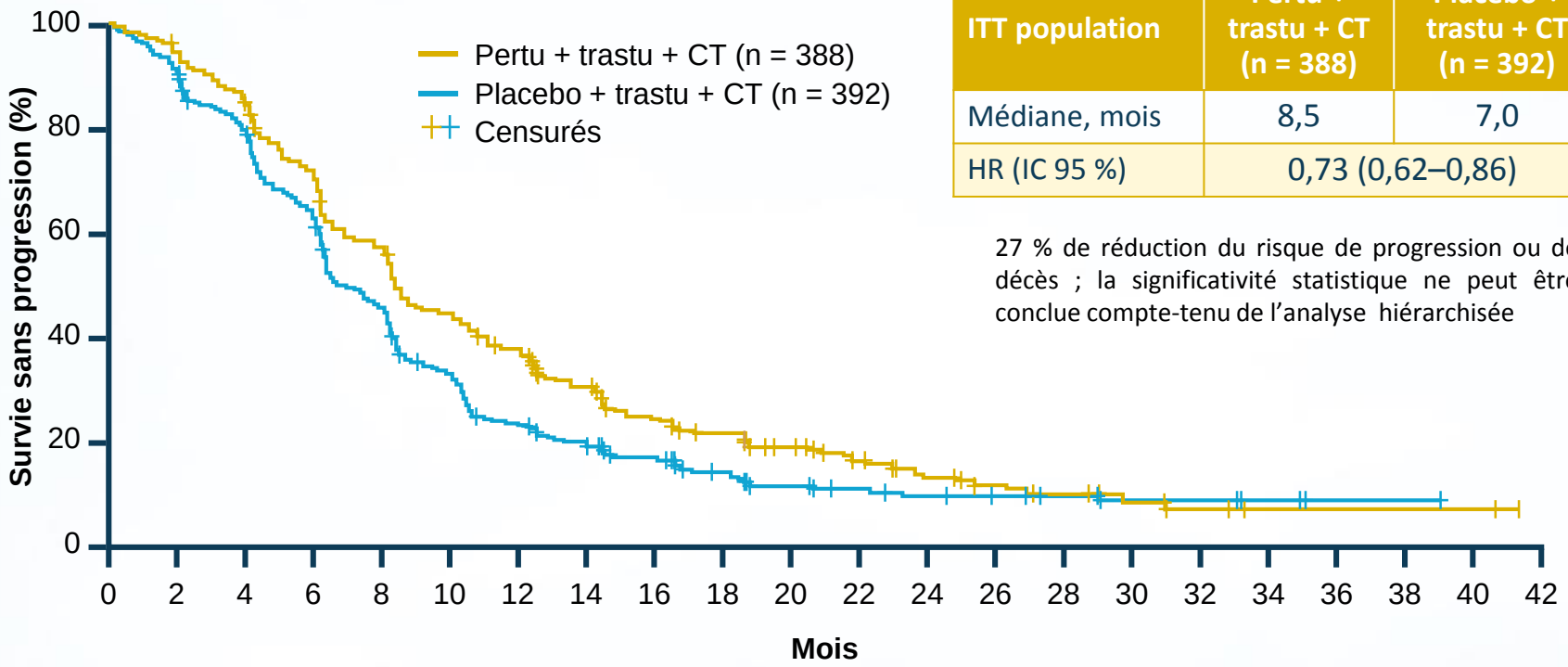


Patients à risque

Pertu	388	363	342	323	297	266	243	209	175	149	114	92	67	54	36	27	16	10	6	4	3
Placebo	392	359	339	306	279	252	221	175	143	118	95	76	60	47	38	31	23	14	7	4	2

- **Médiane de suivi :**
  - Pertu + trastu + CT = 24,4 mois (IC 95 % 22,3–26,1)
  - Placebo + trastu + CT = 25,0 mois (IC 95% 22,3–28,9)

Survie sans progression



ITT population	Pertu + trastu + CT (n = 388)	Placebo + trastu + CT (n = 392)
Médiane, mois	8,5	7,0
HR (IC 95 %)	0,73 (0,62–0,86)	

27 % de réduction du risque de progression ou de décès ; la significativité statistique ne peut être conclue compte-tenu de l'analyse hiérarchisée

Patients à risque

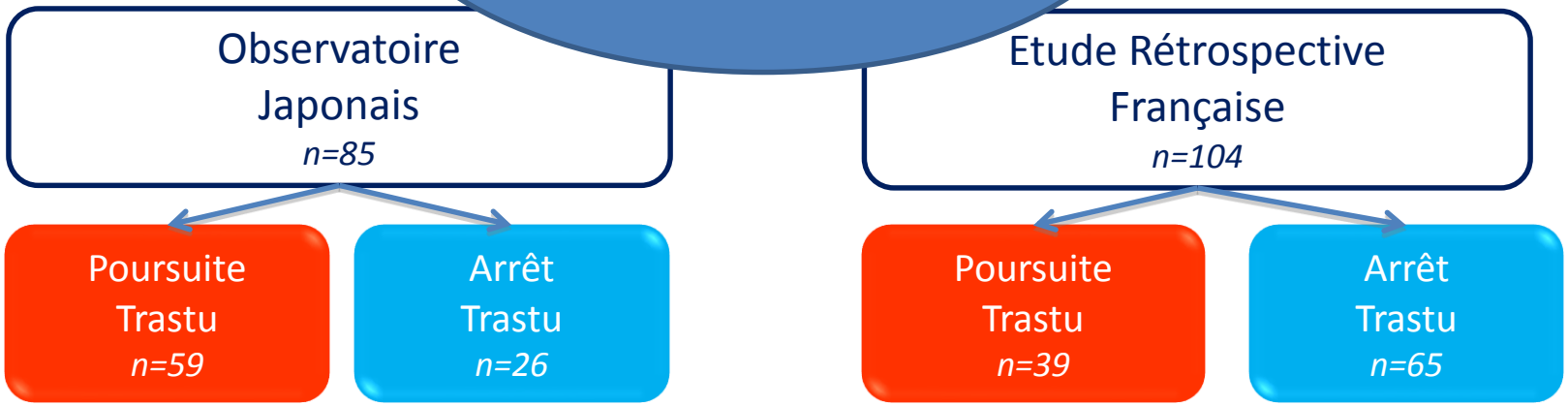
Pertu	388	354	320	267	213	165	135	104	80	67	50	36	26	18	14	7	4	2	2	2	2
Placebo	392	349	301	242	172	120	85	67	51	35	27	21	17	15	12	8	7	4	1	1	

Poursuite Trastuzumab en L2 ?

- Progression après première ligne à base de platine + Trastuzumab chez d… HER2+
  - Quelle att…
    - Poursuit…
    - Arrêt du T…

NON

…ers ASCO GI 2017



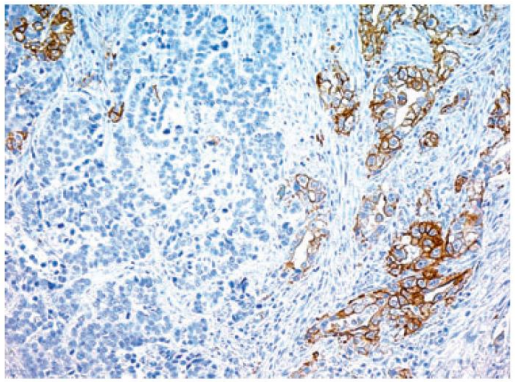
A. Makiyama et al., ASCO GI 2017, Abstract 93; J. Palle et al., ASCO GI 2017, Abstract 94

HER 2 que peut on dire ?

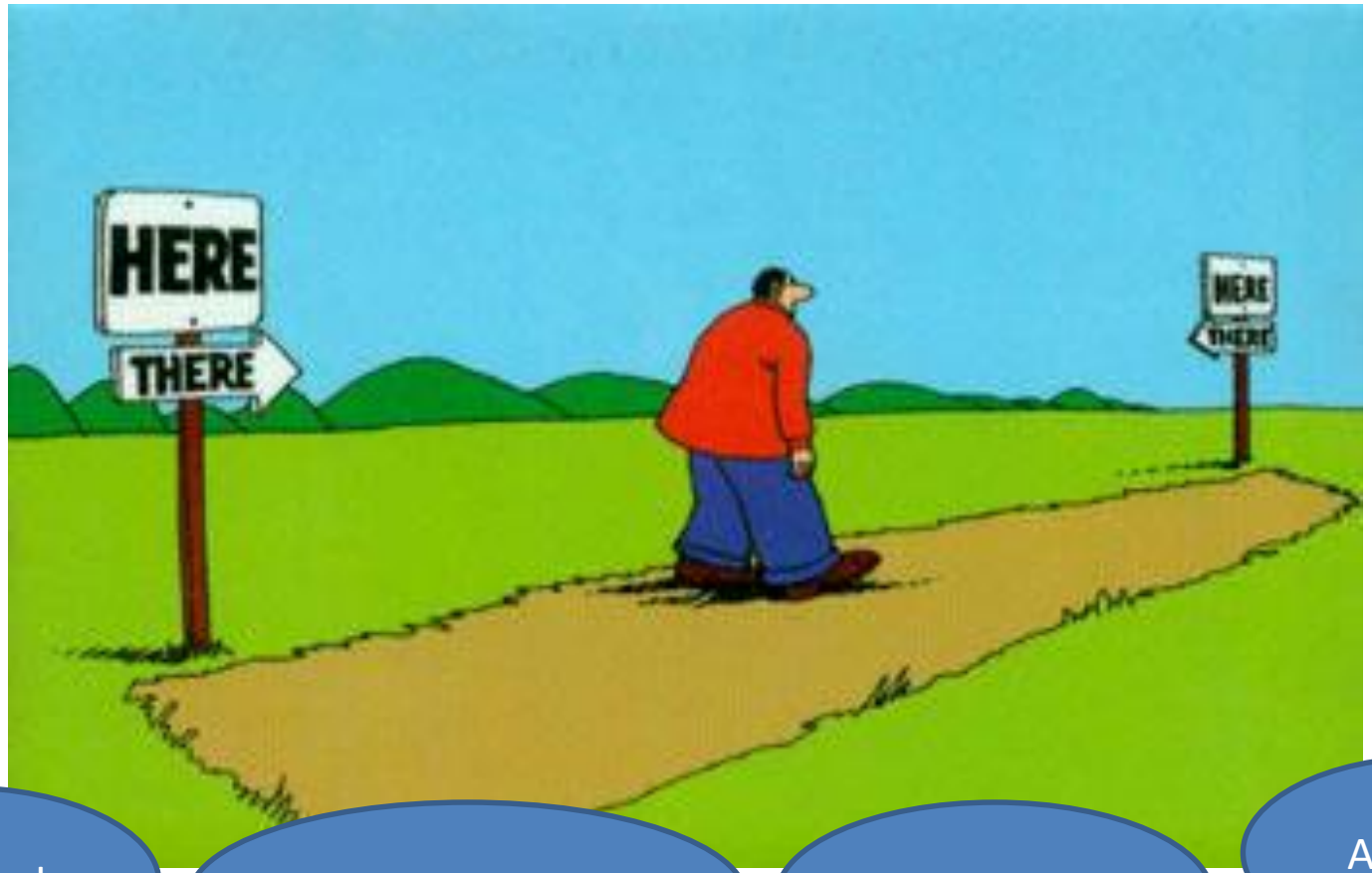
- La négativité successive du TDM1 et de l'essai Jacob (ajout du pertuzumab) nécessite de rechercher prospectivement de nouvelles pistes pour ces patients avec Trastu ?
- Les études avec le Lapatinib en L1 et L2 sont négatives aussi .
- Des essais rétrospectifs, s'appuyant sur une proximité sein et estomac ne sont donc pas opposables.
- L'étude rétrospective FOLFIRI trastuzumab rapportée par l'AGEO à l'ASCO GI ne peut ainsi constituer aucune base solide pour une prescription en pratique courante.
- A l'heure de la liste en sus, le mauvais usage tue l'innovation.
- L'étude pertuzumab périopératoire en cours (INNOVATION), fait poser le problème de poursuivre une étude en localement avancé alors que l'indication en L1 métastatique tombe à l'eau.
- La place pour un essai Rechallenge / HER 2 neg et s'il etait positif ?

La seconde chance ? Propositions d'étude pour le Grand Ouest et au-delà ! Essai TOP (Trastu Og finalement Positif)

- L'I/H de l'estomac est complexe (possibilité de faux négatifs)
- pas assez de matériel
- Hétérogeneite de la tumeur
- Changement de statut au cours
- Population ayant eu au moins 2 ligne et
- diagnostiqué HER2 (-)en L1
- Rebiopsies et recherche HER2 par FISH
- Si fish positif : trastuzumab plus CT (Iri seul ou tax si pas recu; sinon rechallenge par Capecitabine ou TAS /TRASTU s/c



BAD TRIP: 80% are HER2 neg !



cetuximab

panitumumab

Bevacizumab

Anti met

2 nd line : really ?

- Few patients receive a L2 in Europe !!!!
  - 14% (REAL 3), 42% (TOGA), 43% (FFCD 03-07)
- About 75% au Japon (étude SPIRITS)

1er Author / Year	N	Treatment	OS (months)	p
Kang 2012	133 69	Docetaxel/Irinotecan BSC	5.1 3.8	0.009
Hironaka 2013	111 108	Irinotecan Paclitaxel	9.5 8.4	0.38
Ford 2014	84 84	Docetaxel BSC	5.2 3.6	0.002
Fuchs (REGARD) 2014	238 117	Ramucirumab Placebo	5.2 3.8	0.047
Wilke (RAINBOW) 2014	330 335	Paclitaxel + Ramu Paclitaxel + Placebo	9.6 7.4	0.017

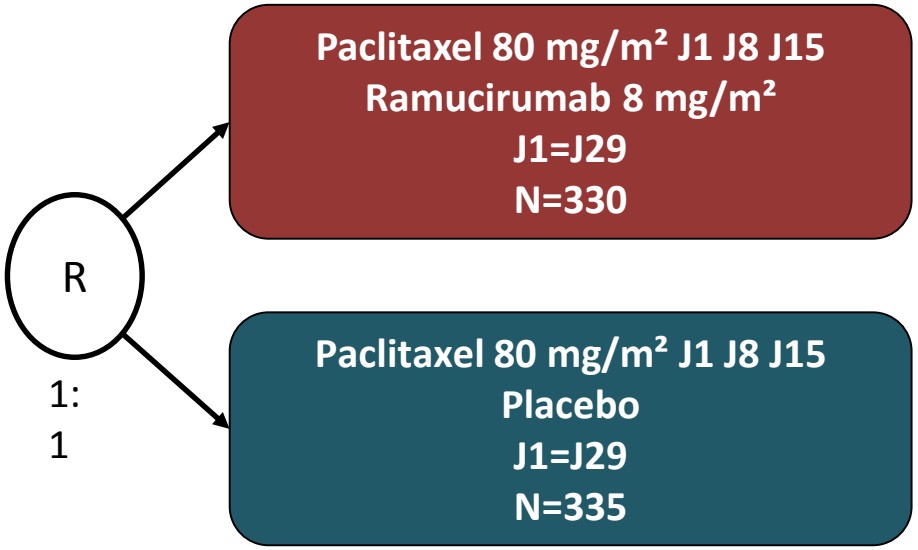
L2 with a new agent?

Ramucirumab + Paclitaxel > Paclitaxel

RAINBOW

- **Ramucirumab: Antibody anti-VEGFR2**
- **double-blind**
- **170 centers from 27 countries**

- 665 pts
- Gastric adenocarcinoma
- L2
- ECOG **0-1**
- **After L1 failure with fluoropyrimidines and platinum**

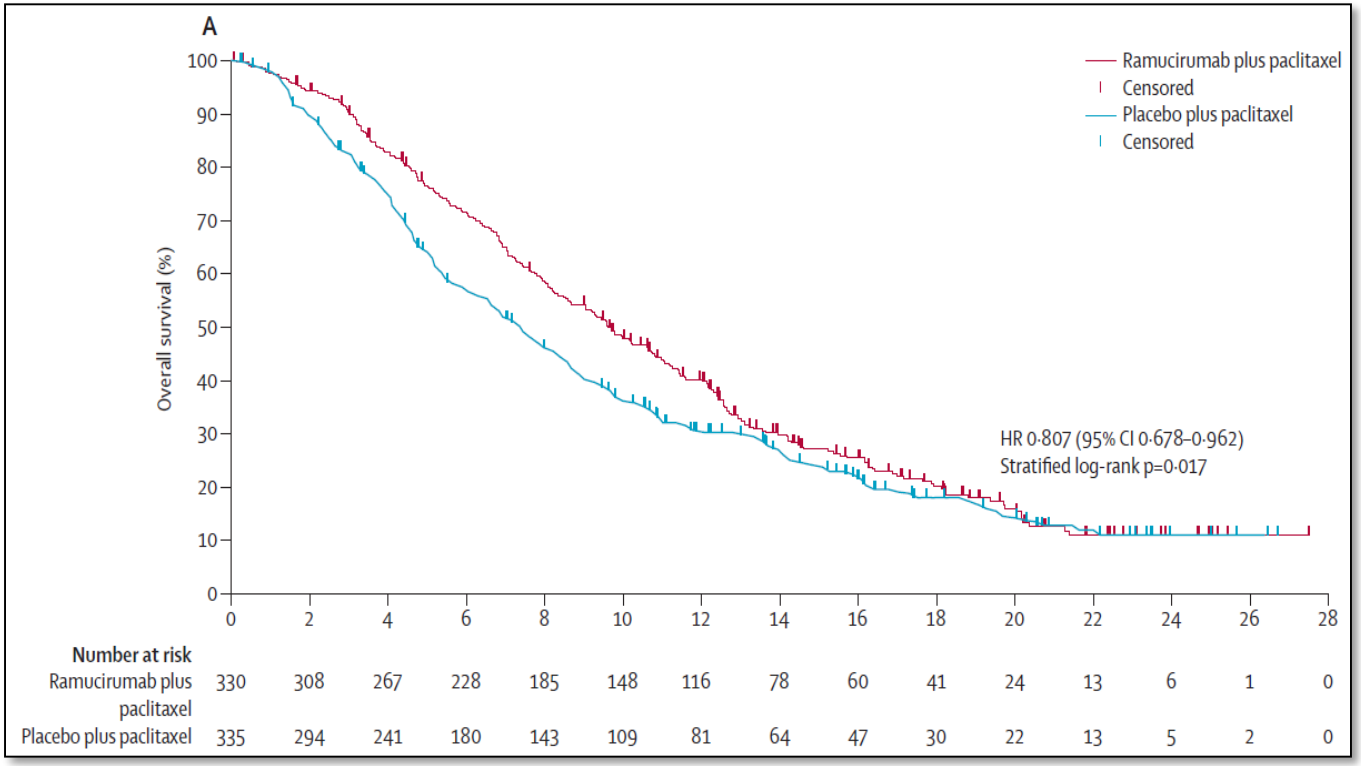


Wilke et al. Lancet Oncol 2014

L2 ?

Ramucirumab + Paclitaxel > Paclitaxel

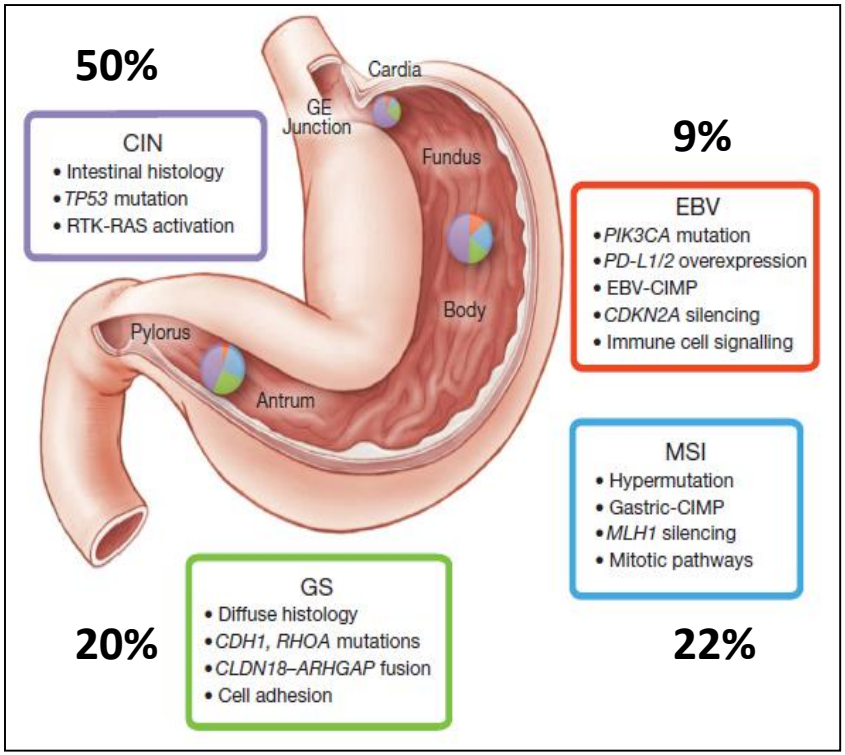
RAINBOW

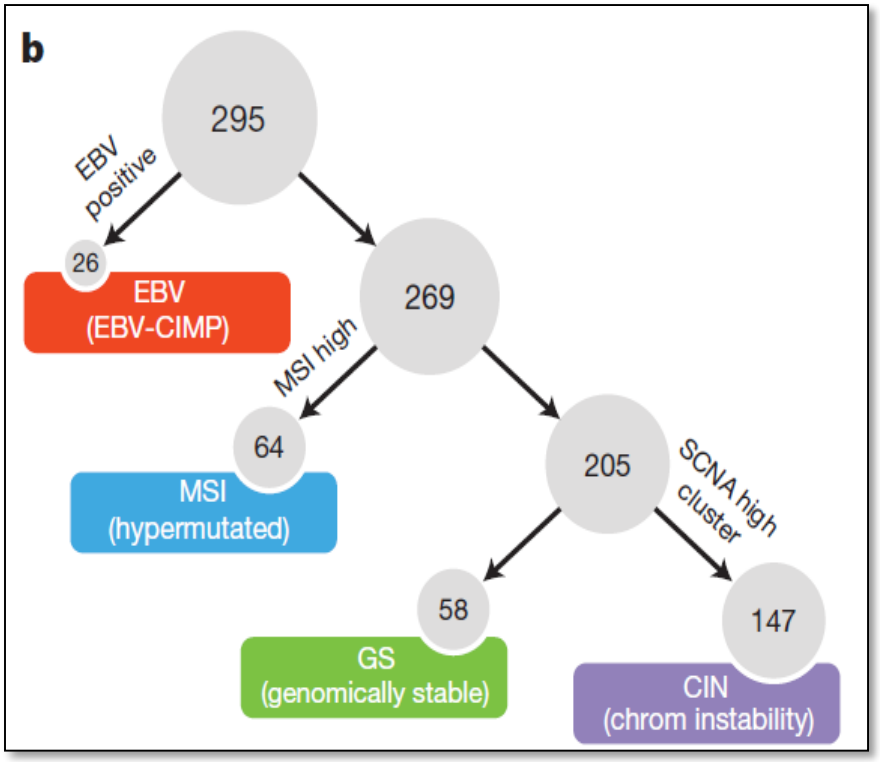


	Ramu + PTX	Placebo + PTX
Médiane (mois) (95%CI)	**9,6 (8,5-10,8)**	**7,4 (6,3-8,4)**
6 months OS **12 months OS**	**72%** **40%**	**57%** **30%**

Wilke et al. Lancet Oncol 201

The future



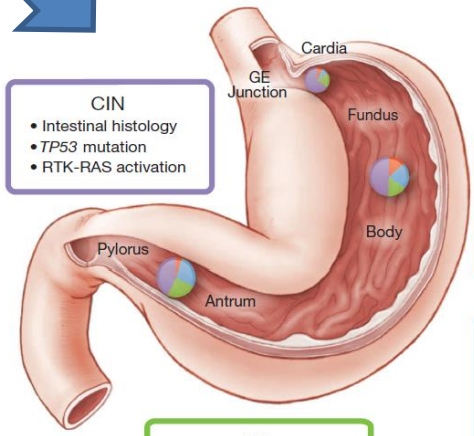


TCGA. Nature 2014

NEXT

Targets

IMMUNOTHERAPY



CIN
- Intestinal histology
- *TP53* mutation
- RTK-RAS activation

EBV
- *PIK3CA* mutation
- *PD-L1/2* overexpression
- EBV-CIMP
- *CDKN2A* silencing
- Immune cell signalling

MSI
- Hypermutation
- Gastric-CIMP
- *MLH1* silencing
- Mitotic pathways

GS
- Diffuse histology
- *CDH1, RHOA* mutations
- *CLDN18–ARHGAP* fusion
- Cell adhesion

CHemotherapy

Immunothérapy

Indication	Statut PDL1	Ligne	Traitement	N	RO (%)	PFS (mois)	OS (mois)	Ref
Gastric	PDL1+	L1+	Pembrolizumab	39	22*	1,9	11,4	Bang, 2016
Gastric, JOG	PDL1 +/-	L1 entr L2	Avelumab	89 62	9 10	3,0 1,5	ND ND	Chung, 2016
Estomac, JOG	PDL1 +/-	L1 entr	Ipilimumab	52	2	2,9	12,7	Moehler 2016
Estomac, JOG, Oeso	PDL1+/-	L2+	Nivolumab Nivo 1 + Ipi 3 Nivo 3 + Ipi 1	59 49 52	14 26 10	1,4 1,5 1,6	5,0 6,9 4,8	Janjigian, 2016
JOG, Œso	PDL1+	L2+	Pembrolizumab	23 (17 CE)	30,4	ND	ND	Doi, 2016

ND : Non déterminé ; NA :non atteint ; L1 entr : traitement d'entretien après 1ère ligne ; JOG : jonction œso-gastrique ;
CE : carcinome épidermoïde ; *22% central review, 33% investigator review

Immuno and Gastric cancer

ID	Ph	Strategy	Indication
NCT02494583 (KEYNOTE 062)	III	Pembrolizumab in monotherapy or in combination with CT	1st Line, HER2-negative, PDL1-positive
NCT02443324	I	Pembrolizumab plus ramucirumab	Specific cohort, 2nd or 3rd line
NCT02335411 (KEYNOTE 059)	II	Pembrolizumab in monotherapy or in combination with CT	Different lines, HER2-negative
NCT02370498 (KEYNOTE 061)	III	Pembrolizumab vs.paclitaxel	2nd line
NCT02563548	I	Pembrolizumab plus PEGPH20	Specific cohort, at least 2nd line
NCT01848834 (KEYNOTE 012)	I	Pembrolizumab	Specific cohort, refractory setting
NCT02452424	I	Pembrolizumab plus PLX3397	Specific cohort, refractory setting
NCT02318901	I/II	Pembrolizumab plus trastuzumab	Specific cohort, HER2-positive
NCT02268825	I/II	Pembrolizumab plus FOLFOX	Specific cohort
NCT02340975	Ib/II	Tremelimumab and/or MEDI4736	Refractory setting
NCT01585987	II	Ipilimumab vs. FU/BSC	Maintenance after 1st line
NCT01928394	I/II	Nivolumab +/- ipilimumab	Specific cohort, refractory setting
NCT02267343	III	Nivolumab	Refractory setting
NCT02488759	I/II	Nivolumab	EBV-positive
NCT01772004	I	Avelumab	Specific cohort, 3rd line
NCT01943461	I	Avelumab	2nd and 3rd line, Japanese and Asian
NCT01633970	I	MPDL3280A monotherapy or in combination with bevacizumab or CT	Basket
NCT01375842	I	MPDL3280A	Basket
NCT02471846	I	MPDL3280A and GDC-0919	Specific cohort, refractory setting

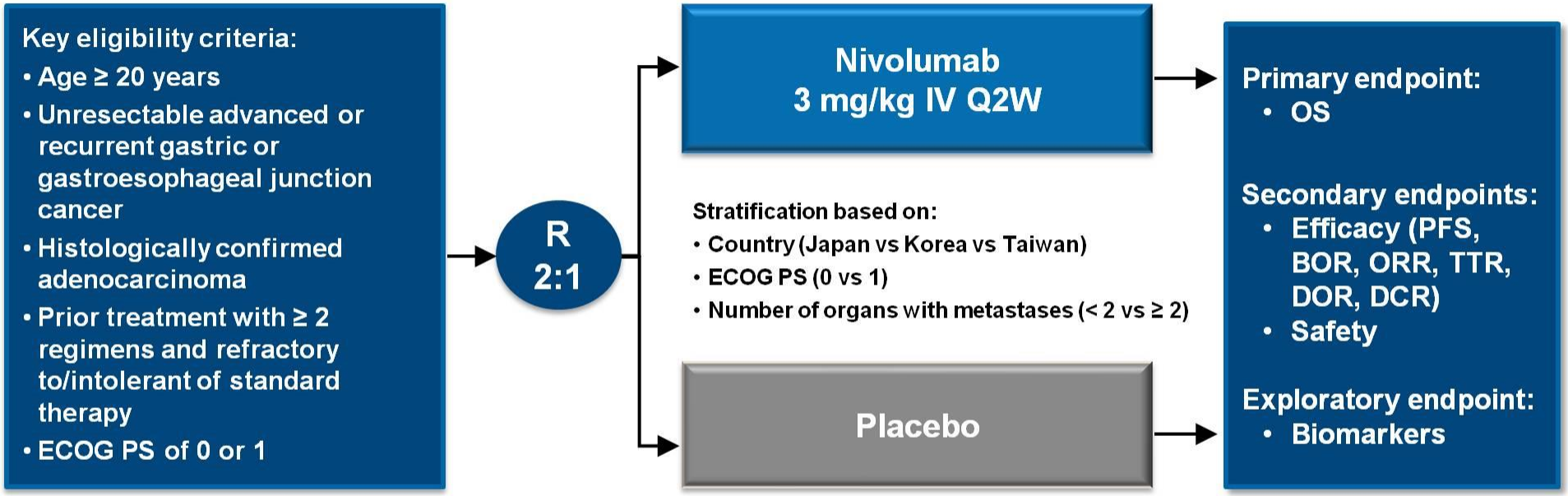
Nivolumab (ONO-4538/BMS-936558) as Salvage Treatment After Second- or Later-Line Chemotherapy for Advanced Gastric or Gastroesophageal Junction Cancer (AGC): A Double-Blinded, Randomized, Phase 3 Trial

Yoon-Koo Kang,[1] Taroh Satoh,[2] Min-Hee Ryu,[1] Yee Chao,[3] Ken Kato,[4] Hyun Cheol Chung,[5] Jen-Shi Chen,[6] Kei Muro,[7] Won Ki Kang,[8] Takaki Yoshikawa,[9] Sang Cheul Oh,[10] Takao Tamura,[11] Keun-Wook Lee,[12] Narikazu Boku,[4] Li-Tzong Chen[13]

[1]Department of Oncology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; [2]Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan; [3]Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan; [4]Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [5]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Song Dang Institute for Cancer Research, Yonsei University College of Medicine, Yonsei University Health System, Seoul, Korea; [6]Division of Hematology/Oncology, Department of Internal Medicine, Linkou Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; [7]Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [8]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [9]Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan; [10]Division of Hematology/Oncology, Internal Medicine Department, College of Medicine, Korea University, Seoul, Korea; [11]Medical Oncology, Kindai University, Faculty of Medicine, Osakasayama, Japan; [12]Division of Hematology/Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea; [13]National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan

PRESENTED AT: 2017 Gastrointestinal Cancers Symposium | #GI17

Study Design and Endpoints



- Patients were permitted to continue treatment beyond initial RECIST v1.1–defined disease progression, as assessed by the investigator, if receiving clinical benefit and tolerating study drug

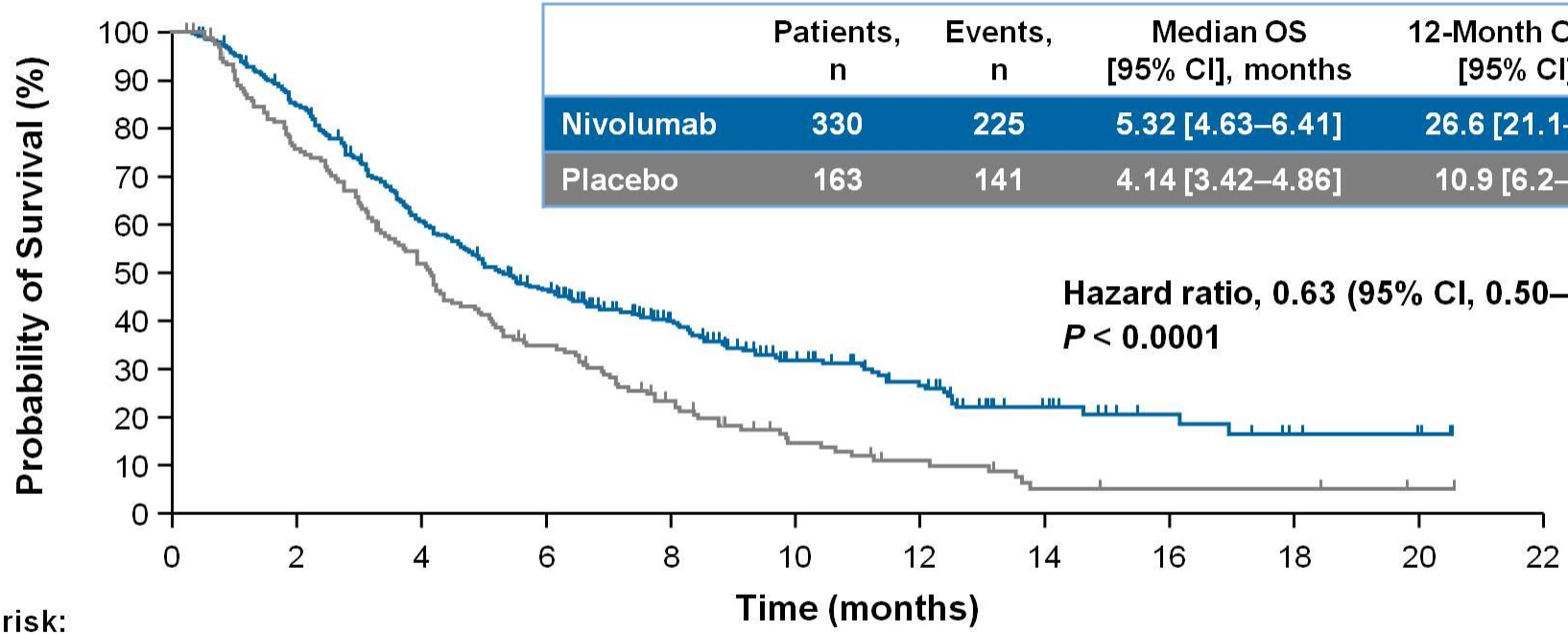
BOR, best overall response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV; intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors; TTR, time to tumor response.

Baseline Characteristics

Characteristic	Nivolumab 3 mg/kg (n = 330)	Placebo (n = 163)
Median age (range), years	62 (20–83)	61 (26–83)
< 65 years, n (%)	189 (57.3)	95 (58.3)
Male, n (%)	229 (69.4)	119 (73.0)
Country, n (%)		
Japan	152 (46.1)	74 (45.4)
Korea	146 (44.2)	74 (45.4)
Taiwan	32 (9.7)	15 (9.2)
ECOG PS, n (%)		
0	95 (28.8)	48 (29.4)
1	235 (71.2)	115 (70.6)
Primary site of disease, n (%)		
Gastric	272 (82.4)	135 (82.8)
Gastroesophageal junction	30 (9.1)	12 (7.4)
Unknown	28 (8.5)	16 (9.8)
Prior gastrectomy, n (%)		
No	133 (40.3)	58 (35.6)
Yes	197 (59.7)	105 (64.4)
Organs with metastases (≥ 2), n (%)	246 (74.5)	119 (73.0)
Prior treatment regimens, n (%)		
2	69 (20.9)	29 (17.8)
3	137 (41.5)	62 (38.0)
≥ 4	124 (37.6)	72 (44.2)
Any prior therapy, n (%)	330 (100)	163 (100)
Fluoropyrimidine	329 (99.7)	163 (100)
Platinum	311 (94.2)	157 (96.3)
Taxane	284 (86.1)	140 (85.9)
Irinotecan	247 (74.8)	123 (75.5)
Ramucirumab	35 (10.6)	22 (13.5)

Overall Survival

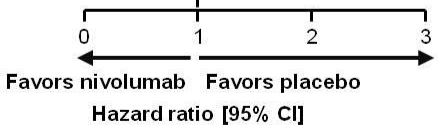
	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	225	5.32 [4.63–6.41]	26.6 [21.1–32.4]
Placebo	163	141	4.14 [3.42–4.86]	10.9 [6.2–17.0]

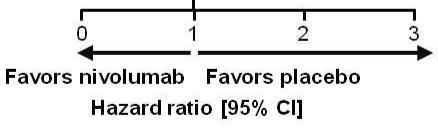


At risk:												
Nivolumab	330	275	193	142	95	57	39	19	10	5	3	0
Placebo	163	121	82	53	32	16	10	4	3	3	1	0

Overall Survival by Subgroup

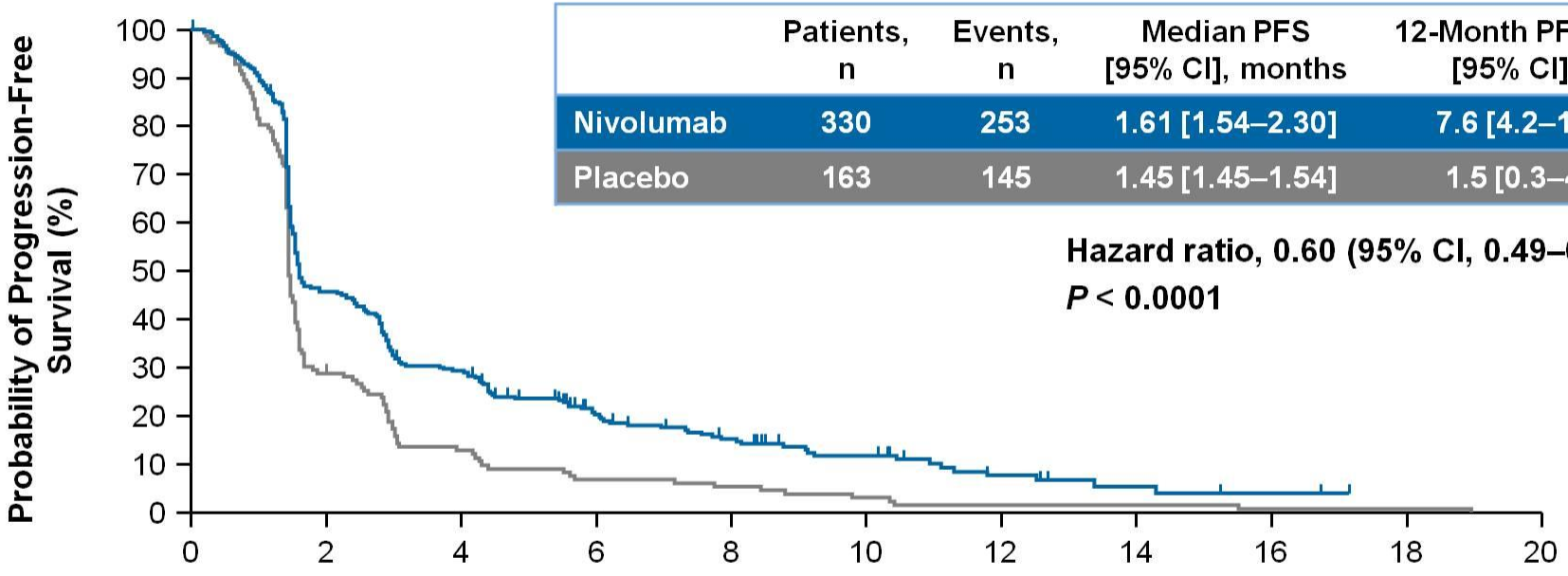
Subgroup	Hazard Ratio [95% CI]
All	0.64 [0.52–0.80]
Country	
Japan	0.63 [0.46–0.85]
Korea	0.70 [0.51–0.96]
Taiwan	0.46 [0.23–0.92]
Age, years	
< 65	0.75 [0.57–0.98]
≥ 65	0.53 [0.38–0.74]
Sex	
Male	0.58 [0.45–0.75]
Female	0.83 [0.56–1.23]
ECOG PS	
0	0.59 [0.40–0.87]
1	0.67 [0.52–0.86]
Prior gastrectomy	
No	0.69 [0.49–0.98]
Yes	0.60 [0.46–0.79]
Primary sites	
Gastric (fundus, corpus, antrum, and pylorus)	0.69 [0.55–0.87]
Gastroesophageal junction	0.44 [0.20–0.97]
Unknown	0.52 [0.26–1.06]
Histological type (Lauren classification)	
Intestinal type	0.59 [0.41–0.85]
Diffuse type	0.82 [0.57–1.17]
Mixed	0.37 [0.13–1.04]
Unknown	0.56 [0.37–0.84]
Number of organs with metastasis	
< 2	0.70 [0.46–1.08]
≥ 2	0.61 [0.48–0.78]
Peritoneal metastasis	
No	0.63 [0.50–0.81]
Yes	0.74 [0.48–1.15]
Liver metastasis	
No	0.63 [0.50–0.80]
Yes	0.67 [0.42–1.07]
Measurable lesion	
No	0.70 [0.43–1.14]
Yes	0.63 [0.50–0.80]
Number of previous regimens	
2	0.82 [0.50–1.35]
3	0.87 [0.61–1.22]
≥ 4	0.44 [0.31–0.61]





Progression-Free Survival

	Patients, n	Events, n	Median PFS [95% CI], months	12-Month PFS Rate [95% CI], %
Nivolumab	330	253	1.61 [1.54–2.30]	7.6 [4.2–12.2]
Placebo	163	145	1.45 [1.45–1.54]	1.5 [0.3–4.8]



Hazard ratio, 0.60 (95% CI, 0.49–0.75)

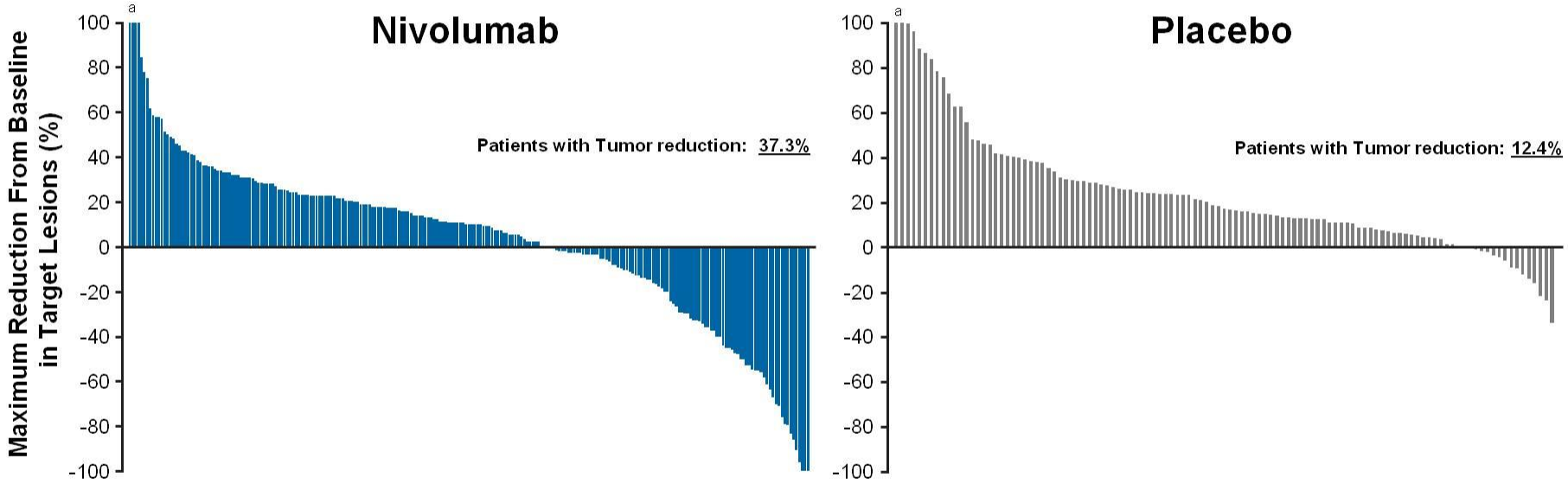
***P* < 0.0001**

At risk:											
Nivolumab	330	131	83	46	31	19	8	4	2	0	0
Placebo	163	41	17	9	7	4	2	2	1	1	0

RECIST Response and Disease Control

	Nivolumab 3 mg/kg (n = 268)	Placebo (n = 131)
ORR, n (%) [95% CI] *P* value	30 (11.2) [7.7–15.6] < 0.0001	0 [0–2.8] —
BOR, n (%) Complete response Partial response Stable disease Progressive disease	 0 30 (11.2) 78 (29.1) 124 (46.3)	 0 0 33 (25.2) 79 (60.3)
DCR, n (%) [95% CI] *P* value	108 (40.3) [34.4–46.4] 0.0036	33 (25.2) [18.0–33.5] —
Median TTR (range), months	1.61 (1.4–7.0)	—
Median DOR, months [95% CI]	9.53 [6.14–9.82]	—

Maximum Reduction in Tumor Burden From Baseline



[a] Patients with a change in tumor burden that exceeds 100%.

Adverse Event Summary

Patients, n (%)	Nivolumab 3 mg/kg (n = 330)		Placebo (n = 161)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
AEs				
Any	300 (90.9)	137 (41.5)	135 (83.9)	63 (39.1)
Serious AEs	131 (39.7)	91 (27.6)	75 (46.6)	47 (29.2)
AEs leading to discontinuation	23 (7.0)	13 (3.9)	12 (7.5)	9 (5.6)
AEs leading to dose delay	63 (19.1)	40 (12.1)	27 (16.8)	17 (10.6)
AEs leading to death	35 (10.6)		25 (15.5)	
TRAEs				
Any	141 (42.7)	34 (10.3)	43 (26.7)	7 (4.3)
Serious TRAEs	33 (10.0)	21 (6.4)	8 (5.0)	4 (2.5)
TRAEs leading to discontinuation	9 (2.7)	4 (1.2)	4 (2.5)	3 (1.9)
TRAEs leading to dose delay	25 (7.6)	14 (4.2)	2 (1.2)	1 (0.6)
TRAEs leading to death	5 (1.5)		2 (1.2)	

AE, adverse event; TRAE, treatment-related adverse event.

Treatment-Related Adverse Events

Patients, n (%)	Nivolumab 3 mg/kg (n = 330)		Placebo (n = 161)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any TRAE	141 (42.7)	34 (10.3)	43 (26.7)	7 (4.3)
TRAEs in > 2% of patients treated with nivolumab				
Pruritus	30 (9.1)	0	9 (5.6)	0
Diarrhea	23 (7.0)	2 (0.6)	3 (1.9)	0
Rash	19 (5.8)	0	5 (3.1)	0
Fatigue	18 (5.5)	2 (0.6)	9 (5.6)	2 (1.2)
Decreased appetite	16 (4.8)	4 (1.2)	7 (4.3)	1 (0.6)
Nausea	14 (4.2)	0	4 (2.5)	0
Malaise	13 (3.9)	0	6 (3.7)	0
AST increased	11 (3.3)	2 (0.6)	3 (1.9)	0
Hypothyroidism	10 (3.0)	0	1 (0.6)	0
Pyrexia	8 (2.4)	1 (0.3)	3 (1.9)	0
ALT increased	7 (2.1)	1 (0.3)	1 (0.6)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

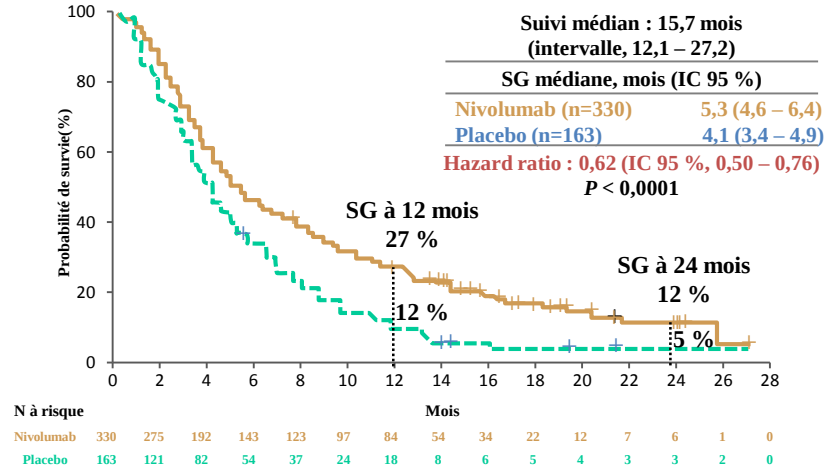
Postprogression Anticancer Therapies

Patients, n (%)	Nivolumab 3 mg/kg (n = 330)	Placebo (n = 163)
Any postprogression therapy	155 (47.0)	72 (44.2)
Radiotherapy	24 (7.3)	15 (9.2)
Surgery	65 (19.7)	28 (17.2)
Pharmacotherapy	115 (34.8)	52 (31.9)
Postprogression pharmacotherapy		
Fluoropyrimidine	30 (9.1)	23 (14.1)
Taxane	28 (8.5)	14 (8.6)
Platinum	18 (5.5)	15 (9.2)
Irinotecan	13 (3.9)	9 (5.5)
Ramucirumab	35 (10.6)	9 (5.5)

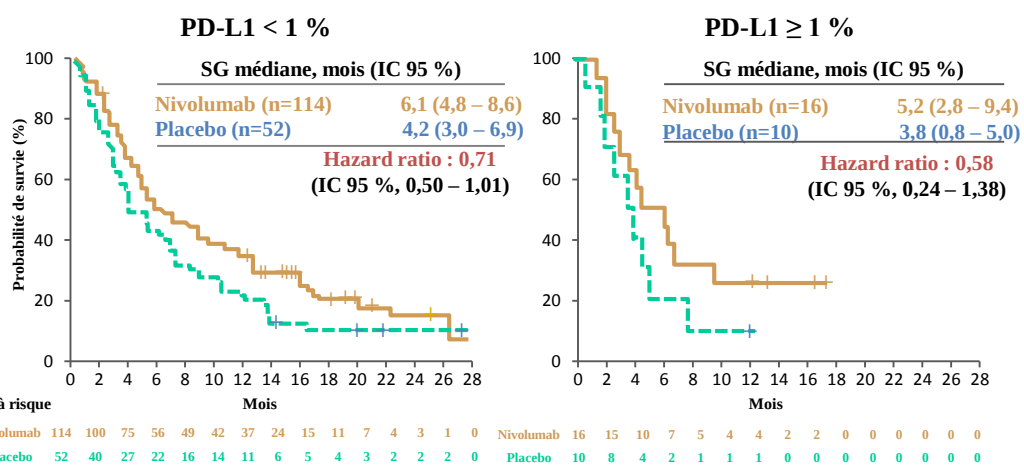
- Postprogression anticancer therapies were similar between arms; few patients received postprogression immunotherapy

Résultats ESMO 2017 !

Survie globale actualisée



Survie globale selon l'expression de PD-L1 < 1 % vs ≥ 1 %



Patients évaluables pour PD-L1 (N=192)

- La phase III « asiatique » (aucun patient caucasien) est **positive**. L'update confirme les résultats déjà présentés à l'ASCO GI et à l'ASCO 2017.
- La présentation de l'étude ancillaire est décevante (absence d'intérêt de l'immunohistochimie telle que pratiquée avec un cut-off à 1 %).

Conclusions

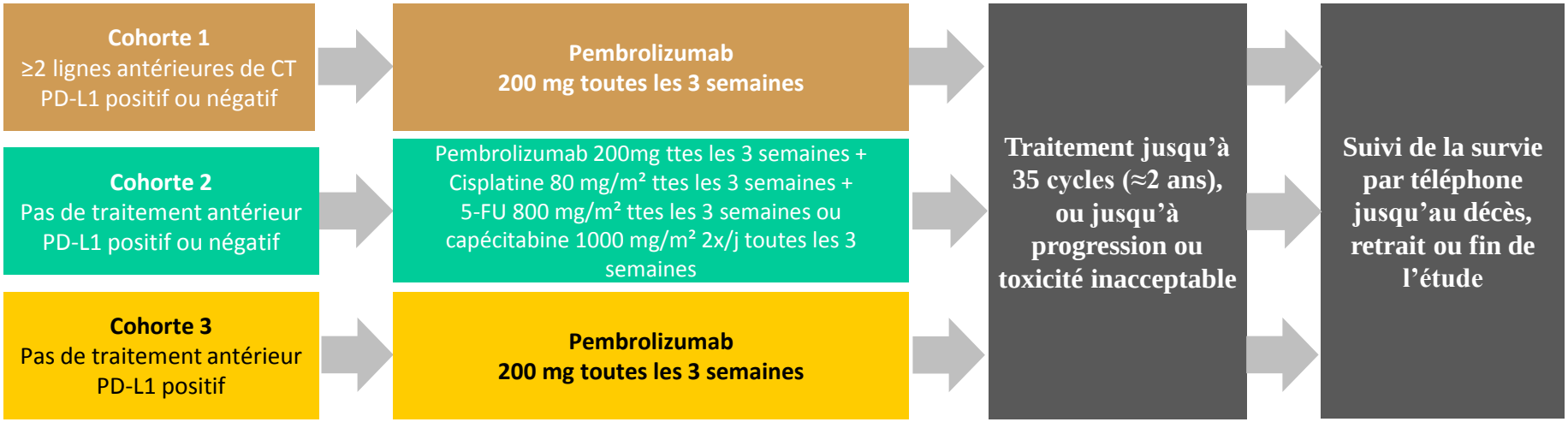
- This phase 3 study demonstrated the efficacy and safety of nivolumab as a third or later line of treatment in patients with AGC
  - Superior OS vs placebo, with long-term survival
  - Superior response rates, disease control, and PFS vs placebo
  - Nivolumab was well tolerated with a safety profile comparable to the placebo arm
- Biomarker analysis is under investigation
- These results indicate that nivolumab could be a new treatment option for patients with heavily pretreated AGC and also provide a strong rationale to explore nivolumab in earlier lines of treatment for gastric cancer

STOP I/H ????

KEYNOTE-059 : Schéma

- Le cancer de la JOG et de l'estomac garde un pronostic effroyable. La médiane de survie reste sous l'année dans les datas des registres français.
- L'arrivée des résultats en terme d'immunothérapie par pembrolizumab (MK 59) et nivolumab (Attraction 02) sont donc très attendus.

Design de KEYNOTE-059

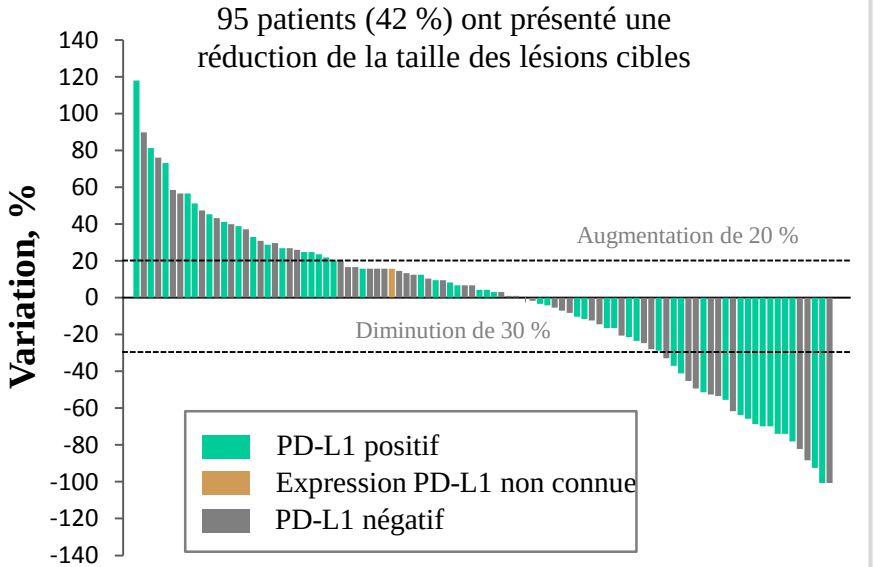


➢ L'étude KEYNOTE-059 est une très importante phase II à plus de 250 patients comprenant 3 cohortes différentes en profil de patient.

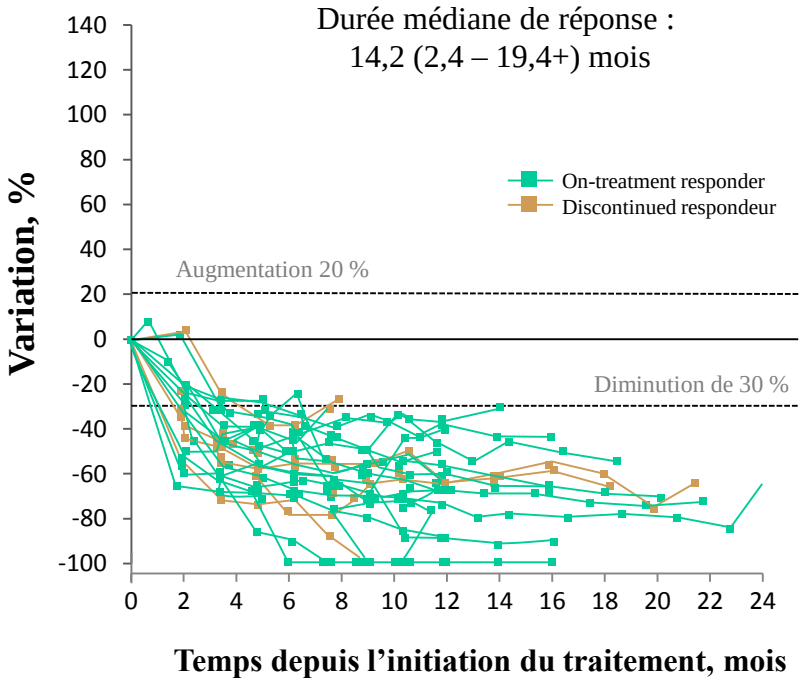
Résultats de la cohorte 1

- Cohorte 1 : Meilleur pourcentage de variation et variation longitudinale de la taille des lésions cibles

Meilleur pourcentage de variation (tous patients) (n = 224)



Variation longitudinale (tous patients) (n = 31)



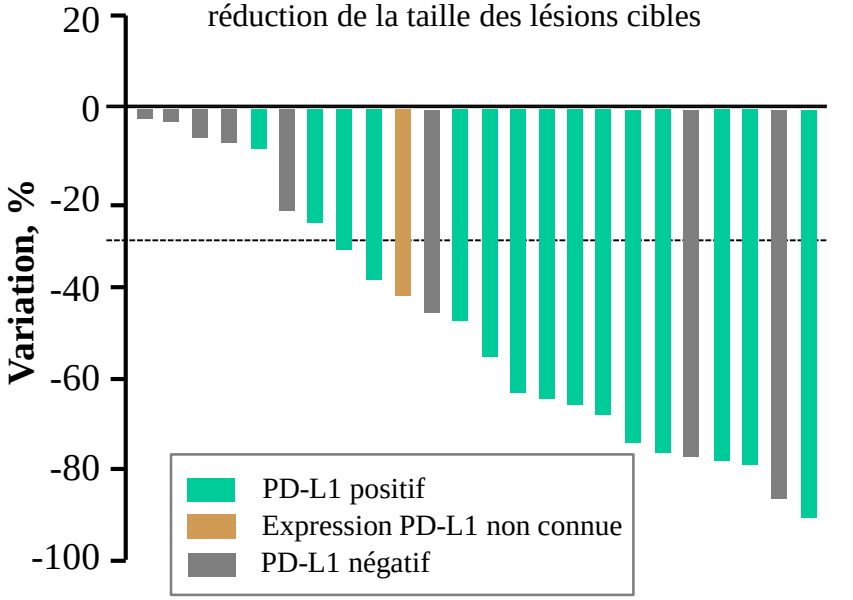
- Patients très fortement pré-traités (plus de 2 lignes)
- Médiane de survie : 5,6 mois
- Taux de régression intéressant

Résultats de la cohorte 2

- Cohorte 2 : Meilleur pourcentage de variation et variation longitudinale de la taille des lésions cibles

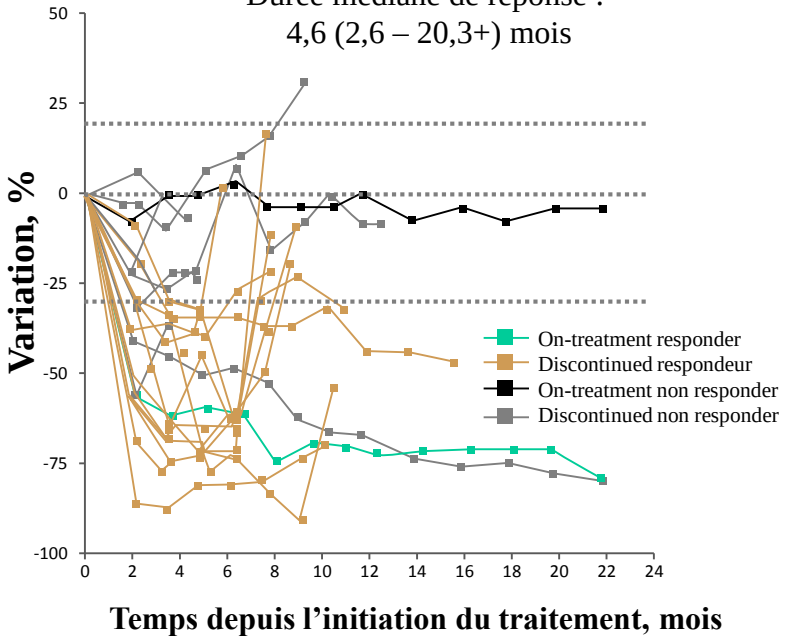
Meilleur pourcentage de variation (tous patients) (n = 24)

24 patients (96 %) ont présenté une réduction de la taille des lésions cibles



Variation longitudinale (tous patients) (n = 25)

Durée médiane de réponse : 4,6 (2,6 – 20,3+) mois

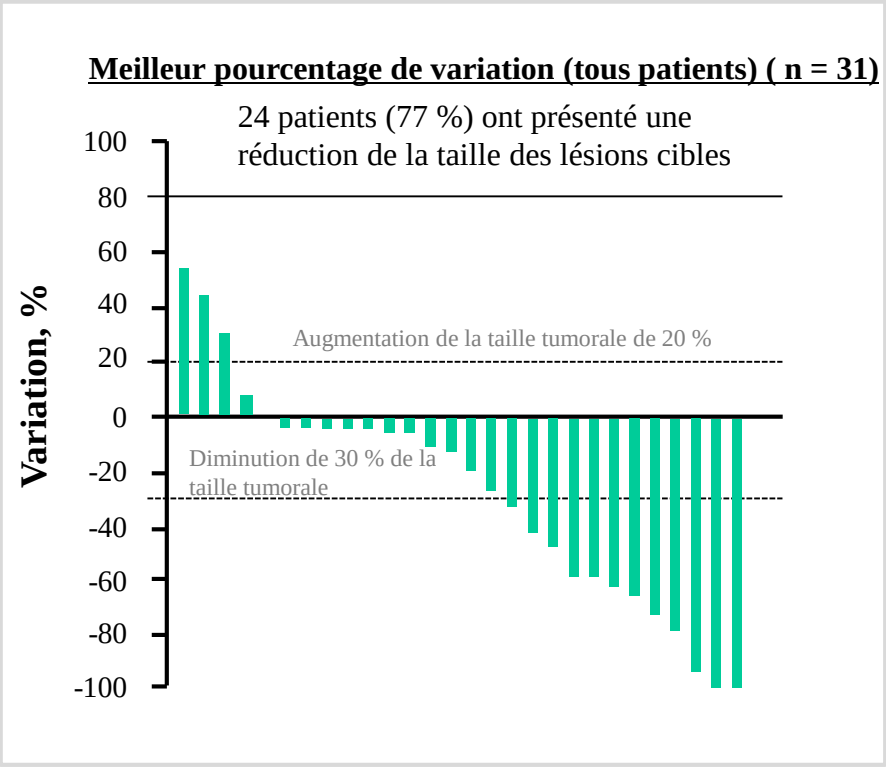


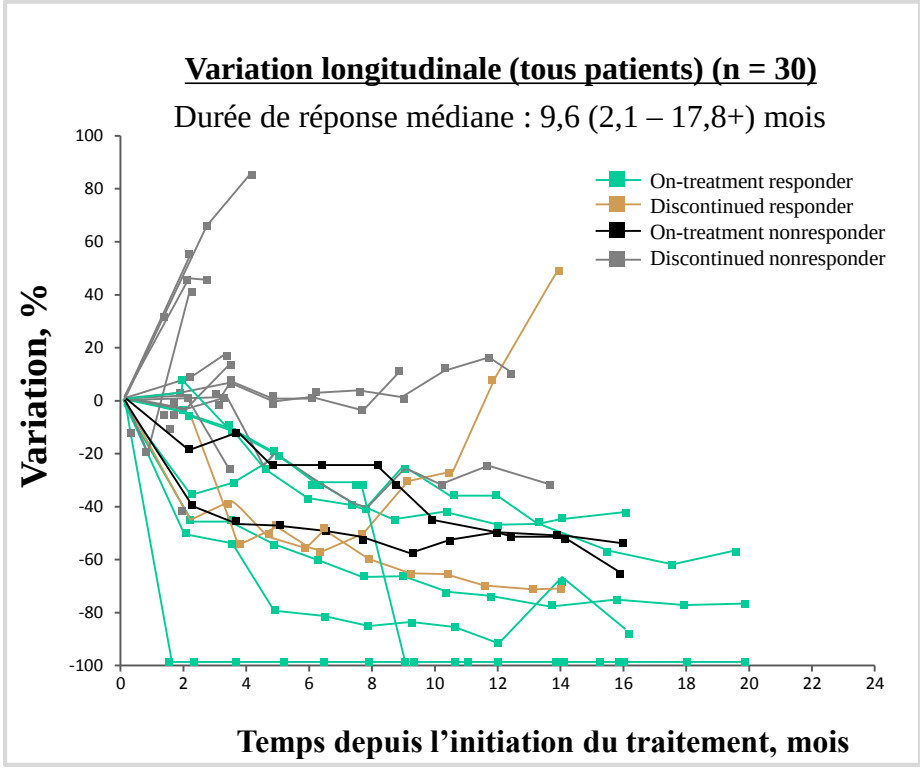
- 96 % de contrôle de la maladie sans effet secondaire ajouté rédhibitoire

→ attente avec impatience des résultats de la phase III

Résultats de la cohorte 3

- Cohorte 3 : Meilleur pourcentage de variation et variation longitudinale de la taille des lésions cibles





- Résultats de contrôle de la maladie à 77 % dans un groupe moins lourdement pré-traité.

Conclusion/Avis d'expert

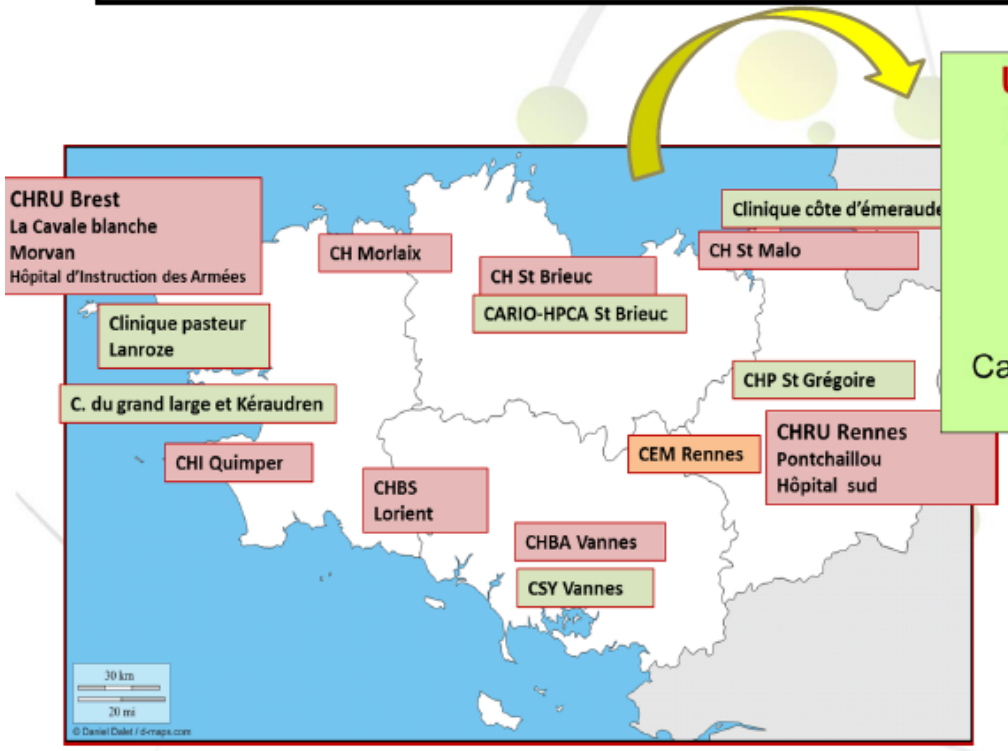
- Les premiers résultats rapportés dans les tumeurs de la jonction œso-gastrique concernaient des séries de quelques dizaines de patients.
- L'étude nivolumab *vs* BSC, bien que concernant des patients asiatiques, apporte pour la 1ère fois une positivité d'un traitement d'immunothérapie *vs* BSC chez des patients lourdement prétraités.
- L'étude KEYNOTE-059, avec une cohorte totale de plus de 250 patients apporte des données sur 3 questions différentes. Au vu de la cohorte la plus importante (cohorte 1) et de son nombre de patients, elle montre un taux de réponse et de stabilisation particulièrement important chez des patients tous lourdement prétraités.
- Vivement des résultats qui confirment la situation.

Les essais !

- Gilead GS US 2013 Nivolumab vs Nivolumab + GS US (MMP9) 120 patients fermés aux inclusions (5 semaines en France).
- Javlin : FOLFOX puis AVE versus CT en L1.
- ……..

De quoi on est parti ?

En Bretagne: Un réseau d'établissements

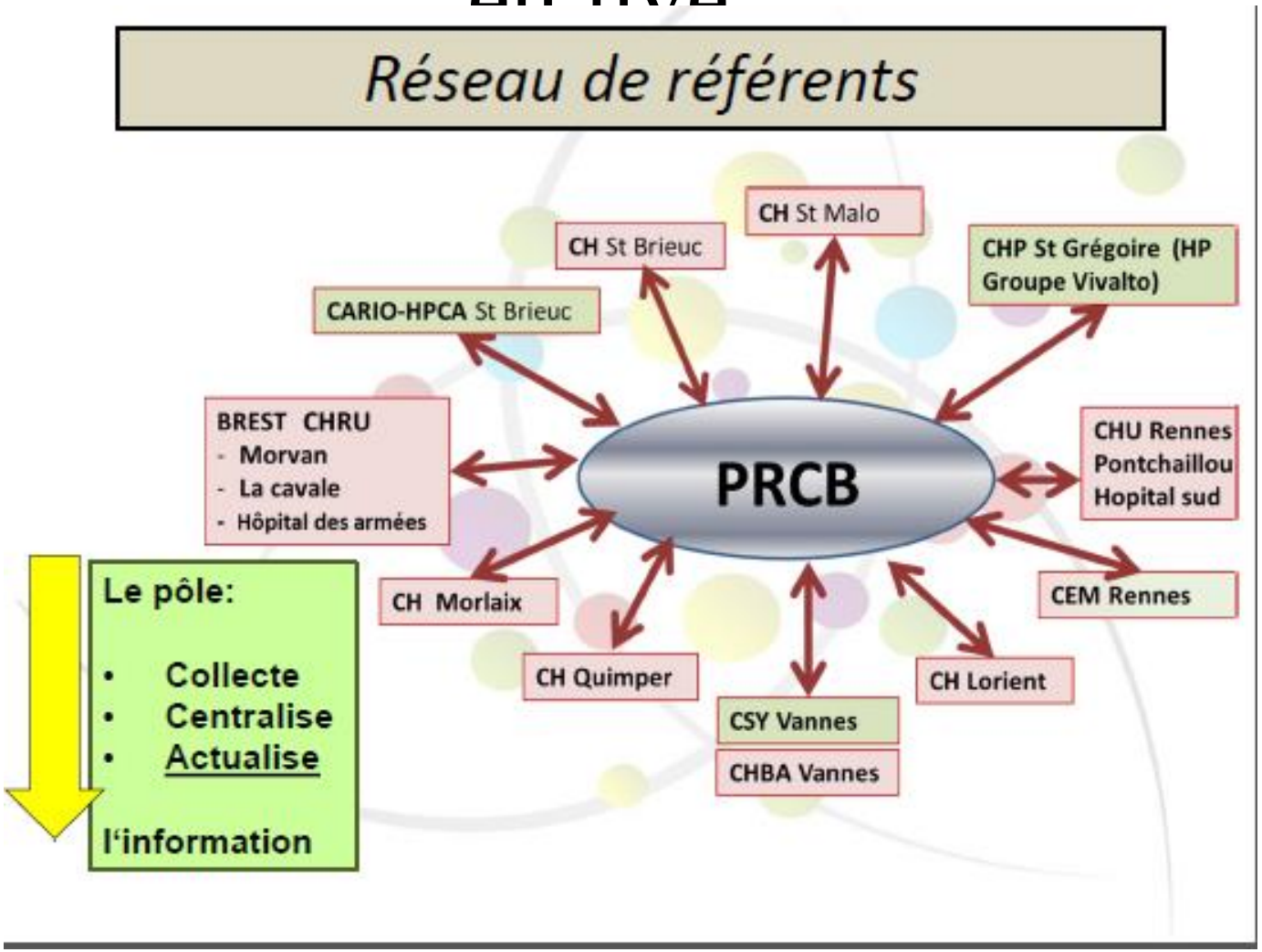


Un Réseau de REFERENTS

Formé de:
TEC
ARC
Chefs de projet
Coordinateurs
Cadres de recherche clinique

18 établissements de soins

Pole régional Bretagne : où est l'essai en live



ORGANISER et mettre en musique le recours : le site accessible à tous !

Our job : the choice