III Simpósio Internacional de Imuno-Oncologia

Tumores Gastrointestinais não-CCR

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São Paulo - SP, 07 de Outubro de 2017

Declaração de Conflitos de Interesse

De acordo com a Resolução 1595 / 2000 do Conselho Federal de Medicina e com a RDC 96 / 2008 da ANVISA, declaro:

- ✓ **Speaker**: Merck, Roche, Janssen, Astellas, Pfizer, Bayer, Ferring e Astrazeneca

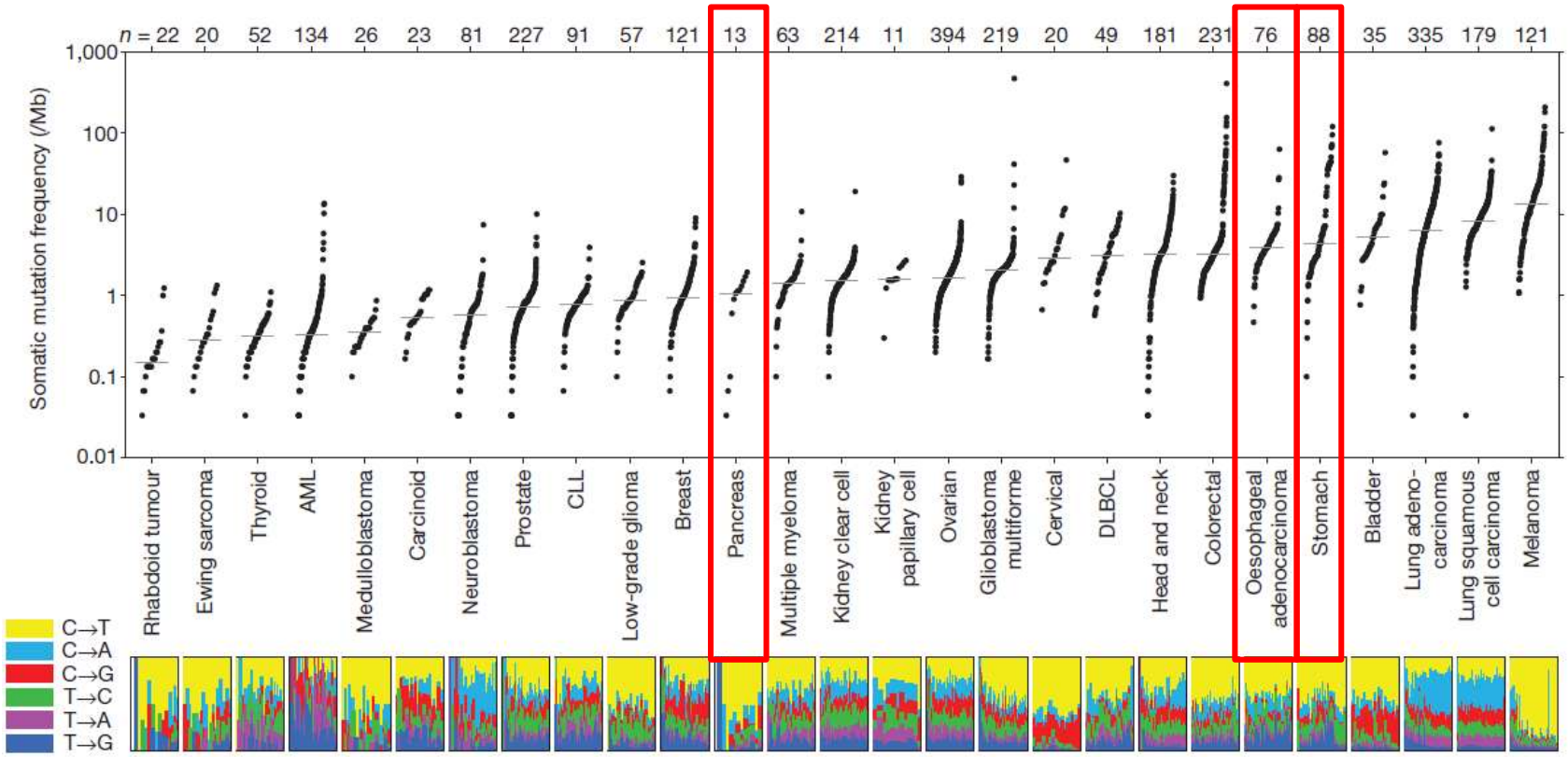
- ✓ **Não** possuo ações em quaisquer destas companhias farmacêuticas

Educação e Pesquisa

Agenda

- ✓ Câncer de Esôfago
- ✓ Câncer de Estômago
- ✓ Hepatocarcinoma

Frequência de Mutações Somáticas



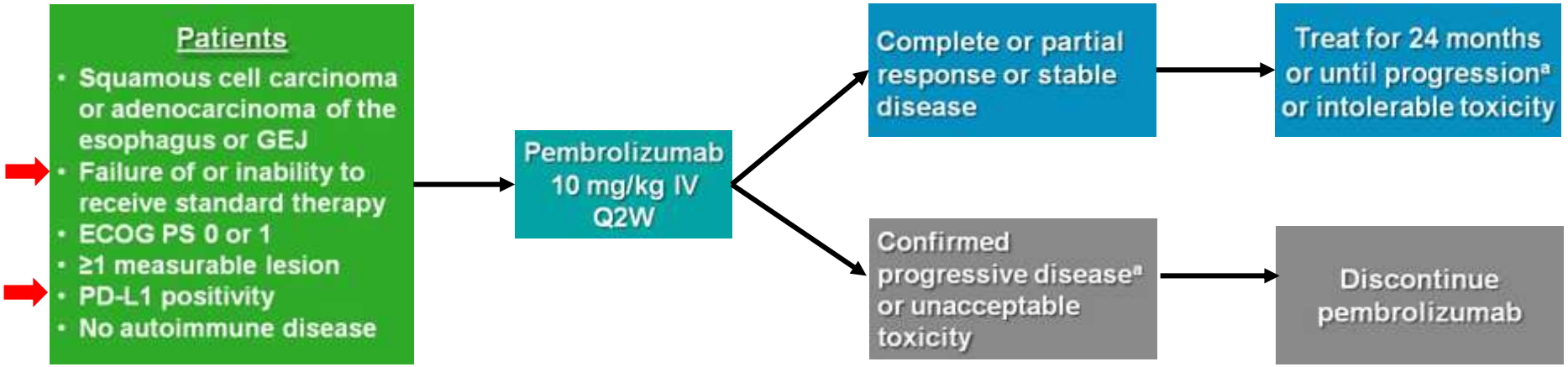
Educação e Pesquisa

Lawrence MS et al. Nature 2013;499(7457):214-218

Câncer de Esôfago

KEYNOTE-028: desenho do estudo

- ✓ **Fase 1b**, Multicoorte, braço único, **n = 23,** coorte de câncer de esôfago pós-falha à terapia-padrão
- ✓ **Pembrolizumabe** nos tumores sólidos **PD-L1 positivo**
- ✓ Positividade de PD-L1 em câncer de esôfago: 41%
- ✓ **End-point 1º: RG**
- ✓ End-point 2º: SLP, SG, duração de resposta, segurança



Educação e Pesquisa

Doi T et al. *ASCO GI* 2016 (abstr 7)

KEYNOTE-028: dados demográficos

Characteristic, n (%)	N = 23
Median age, years (range)	65 (26–71)
Male	19 (83)
Race	
Asian	12 (52)
White	7 (30)
African American/Black	1 (4)
Not specified	3 (13)
ECOG performance status	
0	8 (35)
1	15 (65)
Histology at baseline	
Squamous cell carcinoma	17 (74)
Adenocarcinoma	5 (22)
Mucoepidermoid carcinoma	1 (4)

Characteristic, n (%)	N = 23
Adjuvant or neoadjuvant therapy	6 (26)
Prior lines of therapy for advanced disease	
0	1 (4)
1	2 (9)
2	9 (39)
≥3	11 (48)
Type of prior therapy[a]	
Platinum	23 (100)
Fluoropyrimidine	21 (91)
Paclitaxel	11 (48)
Docetaxel	8 (35)
Epirubicin	3 (13)
Irinotecan	3 (13)
Trastuzumab	1 (4)

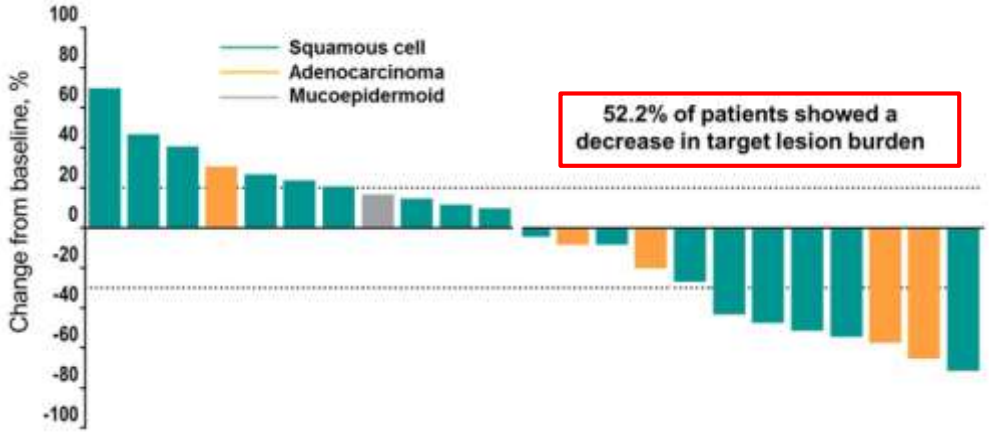
Educação e Pesquisa

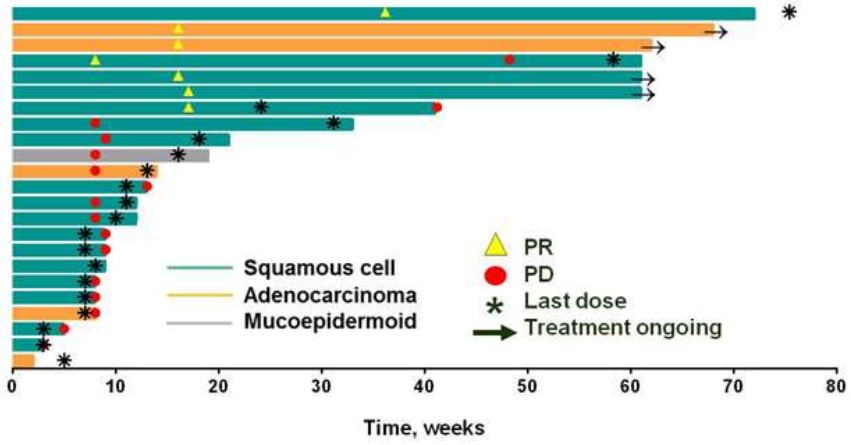
Doi T et al. *ASCO GI* 2016 (abstr 7)

KEYNOTE-028: resposta objetiva e tempo para resposta

Best Overall Response	n	N = 23 %	95% CI
ORR	7	30	13-53
Complete response	0	0	0-15
Partial response	7	30	13-53
Stable disease	2	9	1-28
Progressive disease	13	56	34-77

- ✓ RG por histologia:
- CEC: 29,4% (5/17 pts)
- Adenocarcinoma: 40% (2/5 pts)





- **Tempo para resposta**: 3,7m (1,8-8,3m)
- **Duração de resposta**: NR (5,5-11,8)
- 4 das 7 respostas *ongoing*

Educação e Pesquisa

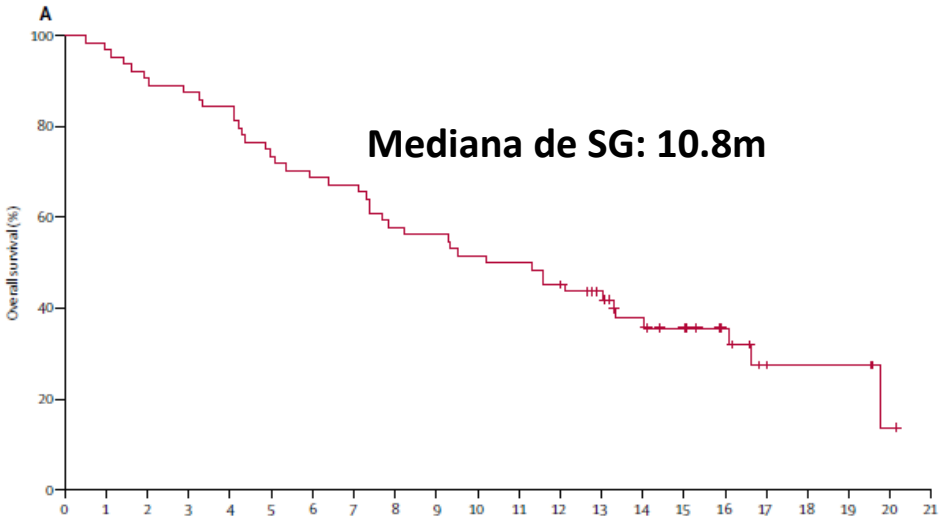
Doi T et al. *ASCO GI* 2016 (abstr 7)

ONO-4538-07

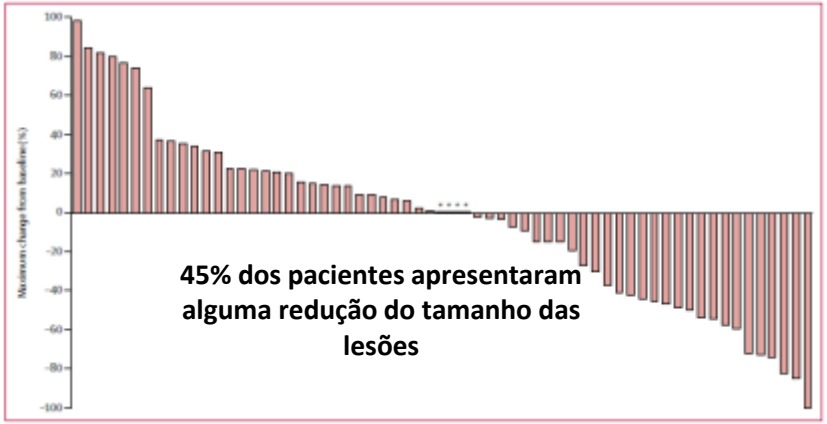
- ✓ **Fase 2**, multicêntrico, braço único, **n=64**
- ✓ **Somente CEC de Esôfago**
- ✓ 68% expostos a **≥ 3 linhas de QT**
- ✓ **Nivolumabe** 3mg/Kg q2w
- ✓ End-point 1º: RG

	Centrally assessed (n=64)	Investigator assessed (n=64)
Best overall response		
Complete response	1 (2%, 95% CI <0·5–8)	2 (3%, 95% CI 1–11)
Partial response	10 (16%, 95% CI 9–26)	12 (19%, 95% CI 11–30)
Stable disease	16 (25%, 95% CI 16–37)	20 (31%, 95% CI 21–43)
Progressive disease	29 (45%)	29 (45%)
Not assessable	8 (13%)	1 (2%)
Objective response*	11 (17%, 95% CI 10–28)	14 (22%, 95% CI 14–33)
Disease controlled†	27 (42%, 95% CI 31–54)	34 (53%, 95% CI 41–65)
Median progression-free survival (months)	1·5 (95% CI 1·4–2·8)	2·3 (95% CI 1·5–3·0)

SG



Mediana de SG: 10.8m



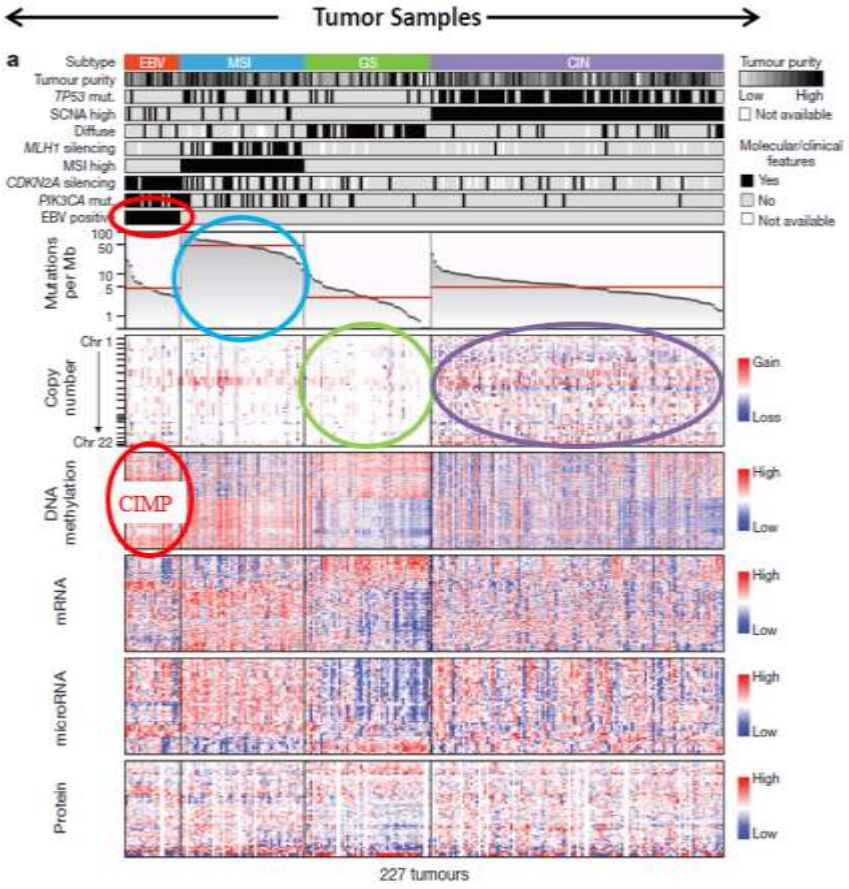
Kudo T et al. *Lancet Oncol 2017;18(*5):631-639

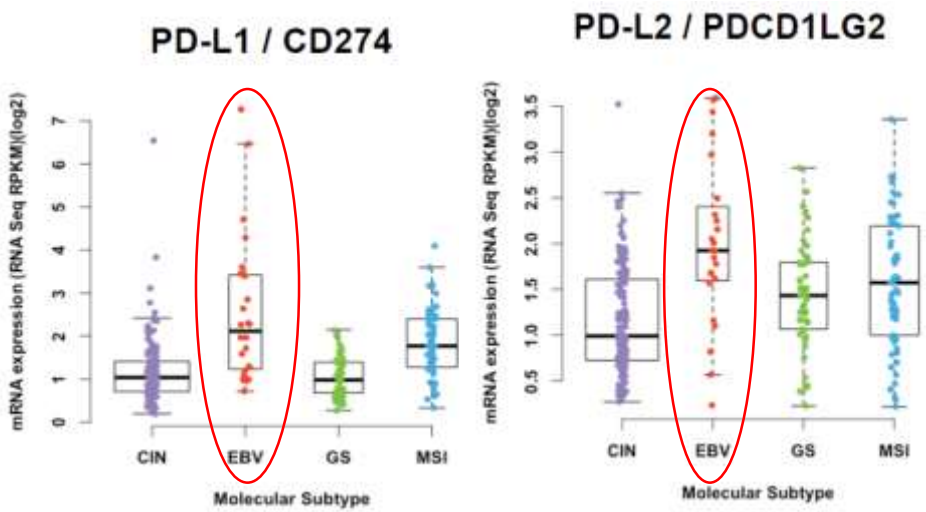
Câncer de Esôfago: estudos em andamento com Inibidores de Checkpoint

Trial	Fase	Histologia	Linha	N	Tratamento
ONO-4538	III	Carcinoma de Esôfago	Falha à QT padrão	390	**Nivolumabe** ou QT isolada
KEYNOTE-180	II	CEC ou Adenocarcinoma de Esôfago ou Adenocarcinoma da JEG Siewert I	≥ 3ª	100	**Pembrolizumabe** isolado
KEYNOTE-181	III	CEC ou Adenocarcinoma de Esôfago ou Adenocarcinoma da JEG Siewert I	2ª	600	**Pembrolizumabe** isolado ou QT isolada
CHECKMATE 577	III	EC II/III carcinoma de esôfago/JEG	Adjuvante (pós-QTRT)	760	**Nivolumabe** ou Placebo

Câncer de Estômago

Câncer de Estômago: caracterização molecular (TCGA)

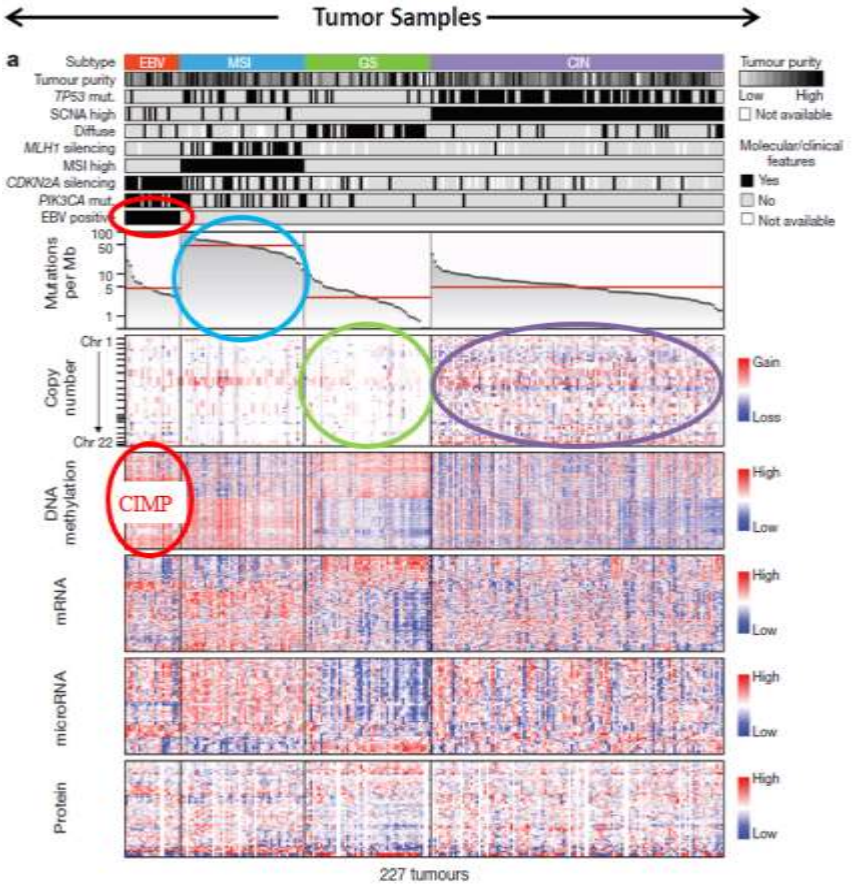


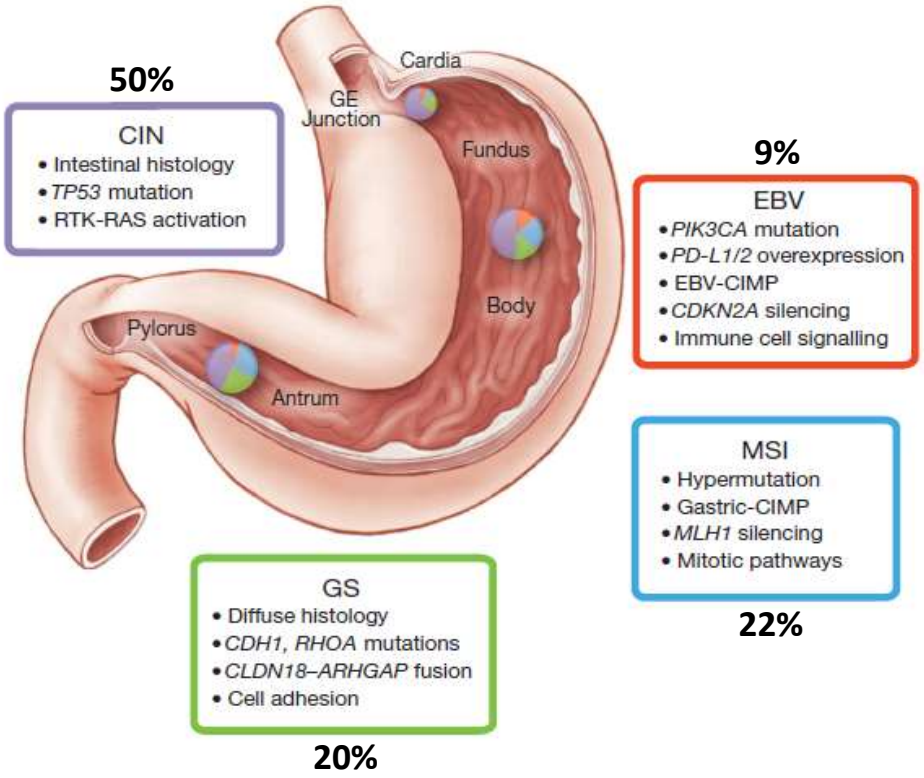


Educação e Pesquisa

The Cancer Genome Atlas Research Network. *Nature* 2014;513:202-9

Câncer de Estômago: caracterização molecular (TCGA)



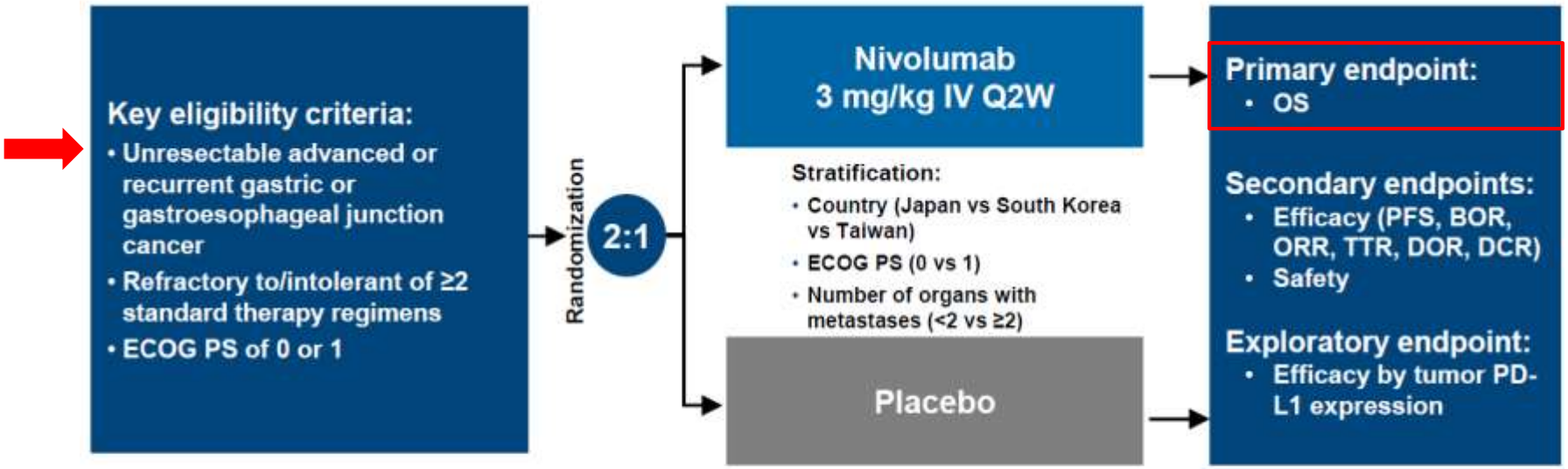


Educação e Pesquisa

The Cancer Genome Atlas Research Network. *Nature* 2014;513:202-9

ATTRACTION-02 (ONO-4538-12): desenho do estudo

- ✓ **Fase 3**, duplo-cego, randomizado, placebo-controlado, n = 493
- ✓ **Somente asiáticos, ≥ 2 linhas de QT, independente do status do PD-L1**



- 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
- Retrospective determination of tumor PD-L1 expression, defined as positive if staining in ≥1% (or ≥5%) of tumor cells, was performed in a central laboratory using immunohistochemistry (28-8 pharmDx assay) for patients with available tumor samples

Educação e Pesquisa

Kang YK et al. *ASCO GI* 2017 (abstr 2)

ATTRACTION-02: características dos pacientes

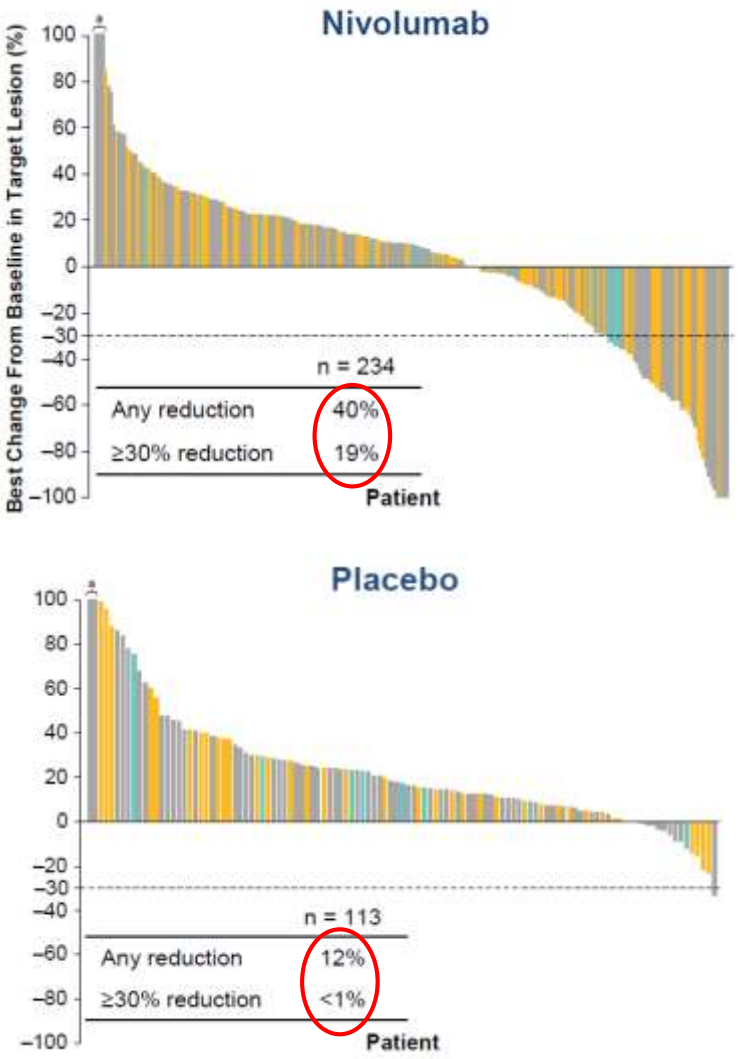
Characteristic	Nivolumab 3 mg/kg (n = 330)	Placebo (n = 163)
Median age (range), years	62 (20–83)	61 (26–83)
< 65 years, n (%)	189 (57.3)	95 (58.3)
Male, n (%)	229 (69.4)	119 (73.0)
Country, n (%)		
Japan	152 (46.1)	74 (45.4)
Korea	146 (44.2)	74 (45.4)
Taiwan	32 (9.7)	15 (9.2)
ECOG PS, n (%)		
0	95 (28.8)	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)

Kang YK et al. *ASCO GI* 2017 (abstr 2)

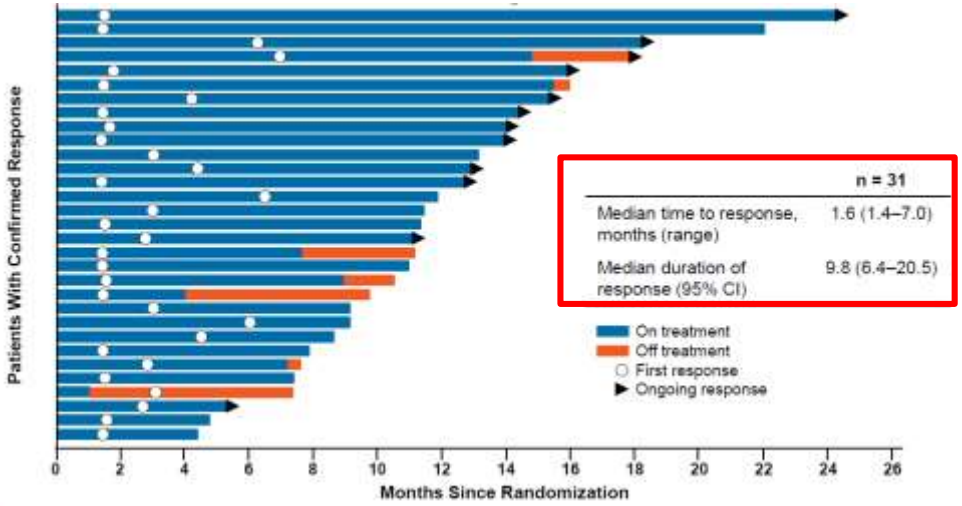
ATTRACTION-02: eficácia (atualizado)

	Nivolumab N = 268	Placebo N = 131
ORR, n (%)	31 (12)	0
95% CI	8–16	0–2.8
P value	<0.0001	
BOR, n (%)		
CR	0	0
PR	31 (12)	0
SD	77 (29)	33 (25)
PD	124 (46)	79 (60)
Not evaluable	36 (13)	19 (15)
DCR, n (%)	108 (40)	33 (25)
95% CI	34.4–46.4	18.0–33.5
P value	0.0036	

Redução das lesões



Tempo para resposta e Duração de resposta

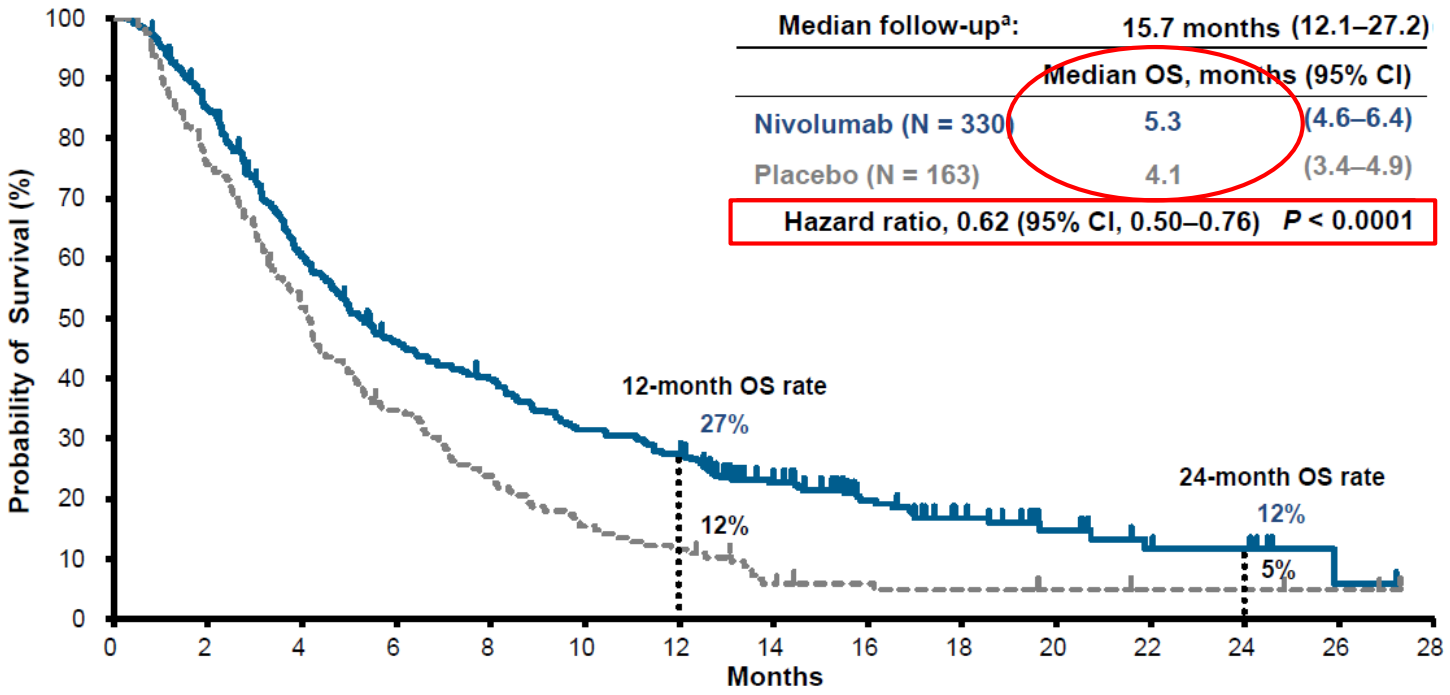


Educação e Pesquisa

Boku N et al. *ESMO 2017* (abstr 617O)

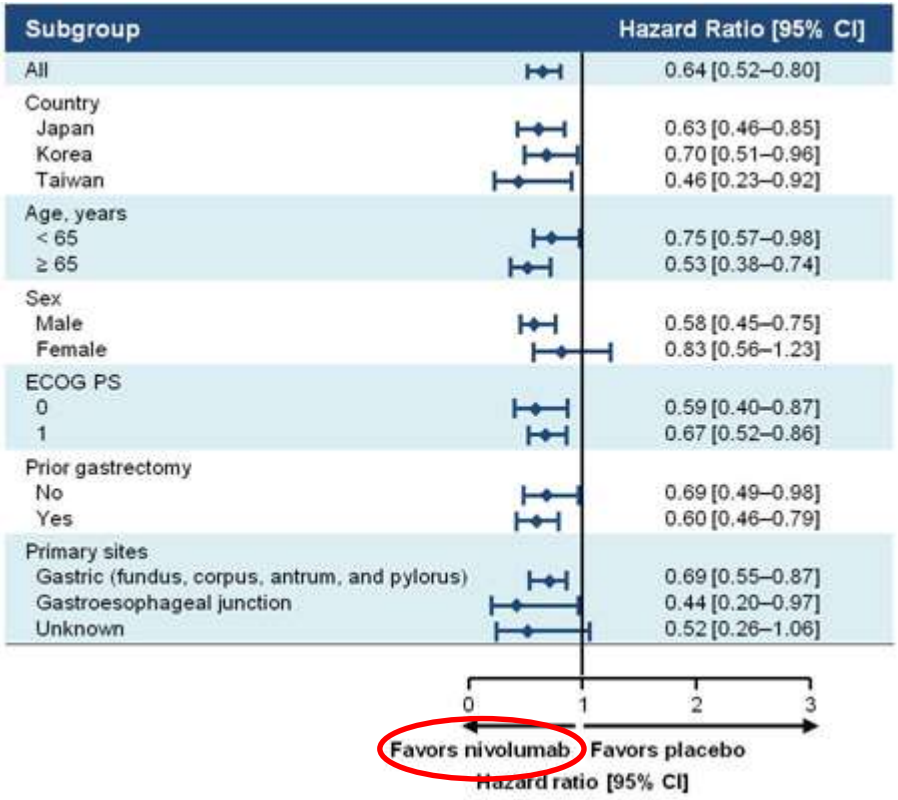
ATTRACTION-02: SG atualizada

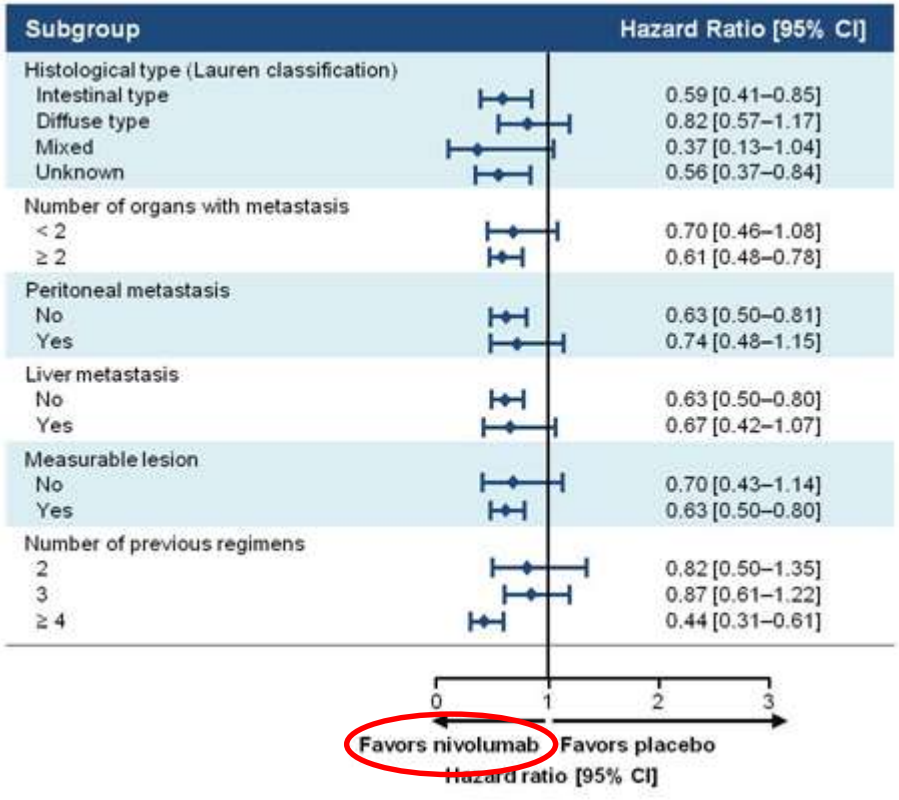
Redução estatisticamente significativa **de 38%** no risco de morte



Boku N et al. *ESMO* 2017 (abstr 617O)

ATTRACTION-02: benefício em SG em todos os subgrupos



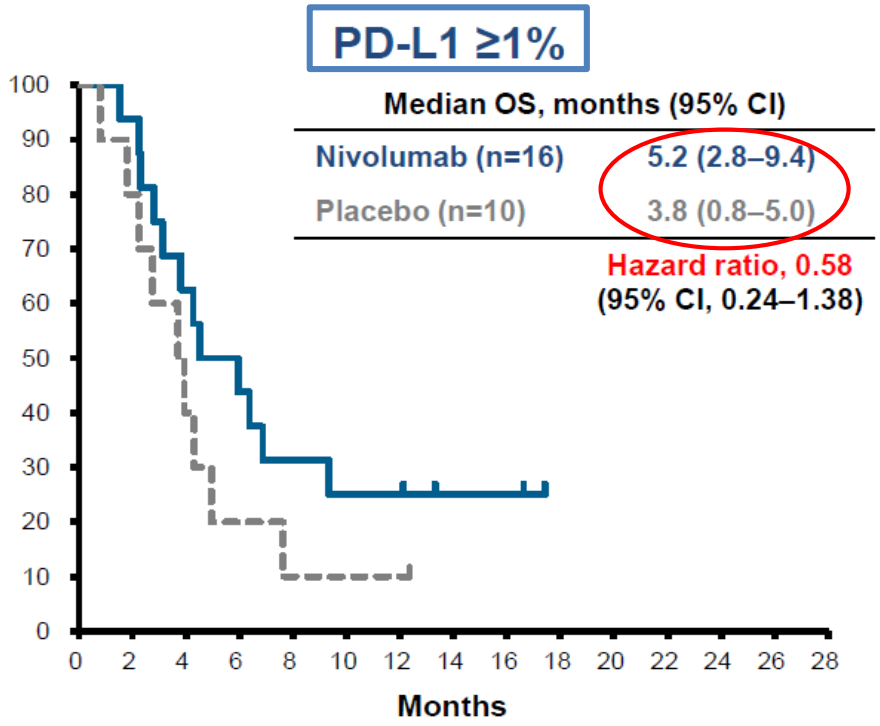


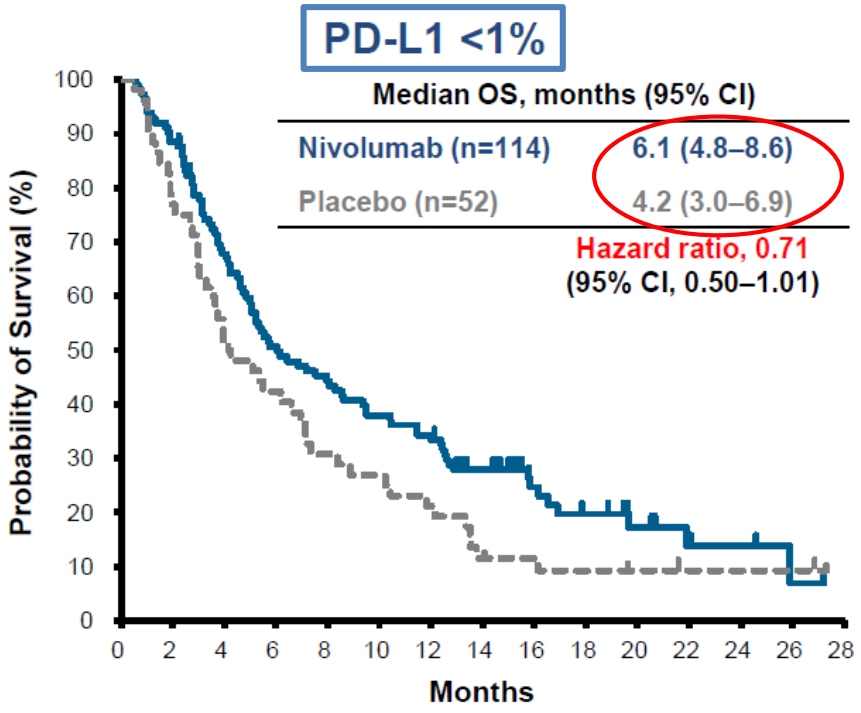
Kang YK et al. *ASCO GI* 2017 (abstr 2)

ATTRACTION-02: benefício em SG independe do status do PD-L1

MADRID 2017 ESMO congress

Análise retrospectiva



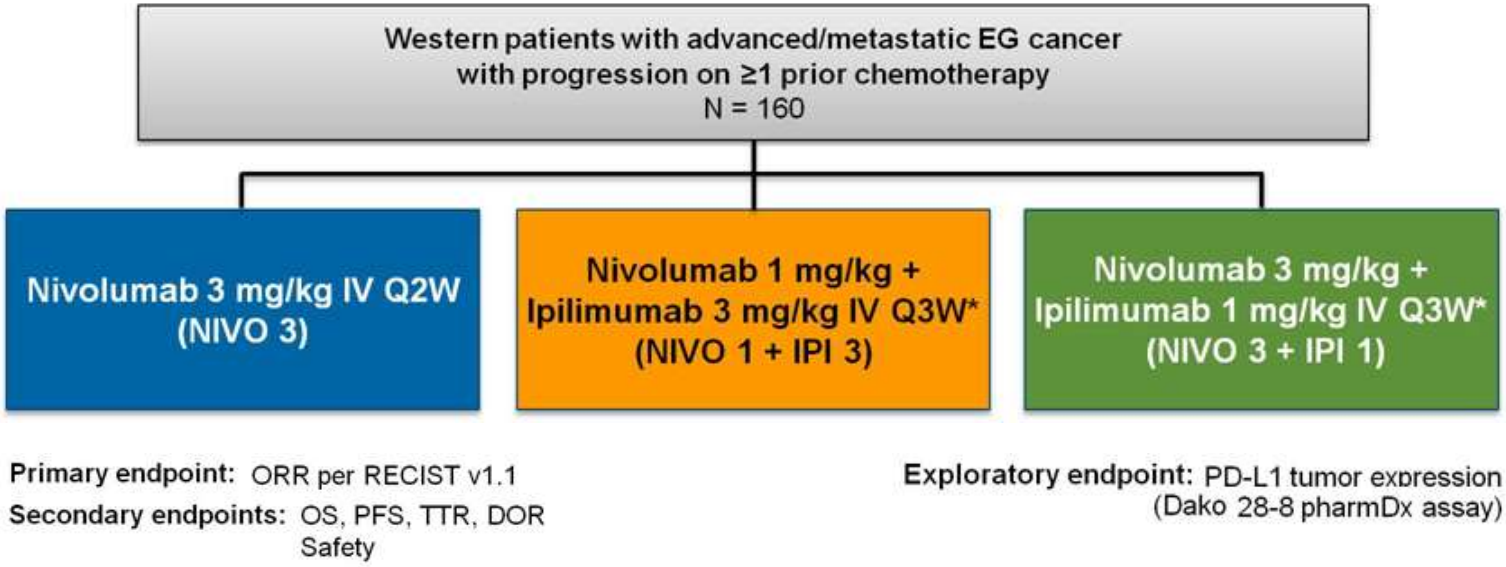


Educação e Pesquisa

Boku N et al. *ESMO* 2017 (abstr 617O)

CHECKMATE-032: anti-PD1 + anti-CTLA4

- ✓ **Fase 1/2**, randomizado, **multi-tumor *coorte***, **população ocidental**, n=160
- ✓ Coorte de Câncer Gástrico, esôfago e JEG, **≥ 1 linha**
- ✓ **independente do status do PD-L1**
- ✓ ***End-point* primário**: Resposta global (RG)
- ✓ Tratamento: 4 ciclos em cada braço seguido de nivolumabe 3 mg/kg q2w até PD ou toxicidade limitante



Janjigian Y et al. *ASCO* 2017; Le D et al. *ASCO GI* 2016

CHECKMATE-032: características dos pacientes

Patients, n (%)	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
Age, median (range), years	60 (29 to 80)	53 (27 to 77)	58 (19 to 81)
≥65 years	17 (29)	10 (20)	17 (33)
Male	45 (76)	34 (69)	45 (87)
Race			
White	56 (95)	46 (94)	50 (96)
Black	3 (5)	1 (2)	1 (2)
Asian/other	0	2 (4)	1 (2)
Primary site			
Gastric	19 (32)	22 (45)	18 (35)
GEJ/esophageal	40 (68)	27 (55)	34 (65)
Number of prior regimens			
0	0	1 (2)	0
1	10 (17)	6 (12)	16 (31)
2	**20 (34)**	**19 (39)**	**16 (31)**
3	**19 (32)**	**11 (22)**	**13 (25)**
>3	**10 (17)**	**12 (24)**	**7 (13)**
PD-L1 tumor expression, n/N (%)*			
≥1%	16/42 (38)	10/42 (24)	13/43 (30)
<1%	**26/42 (62)**	**32/42 (76)**	**30/43 (70)**

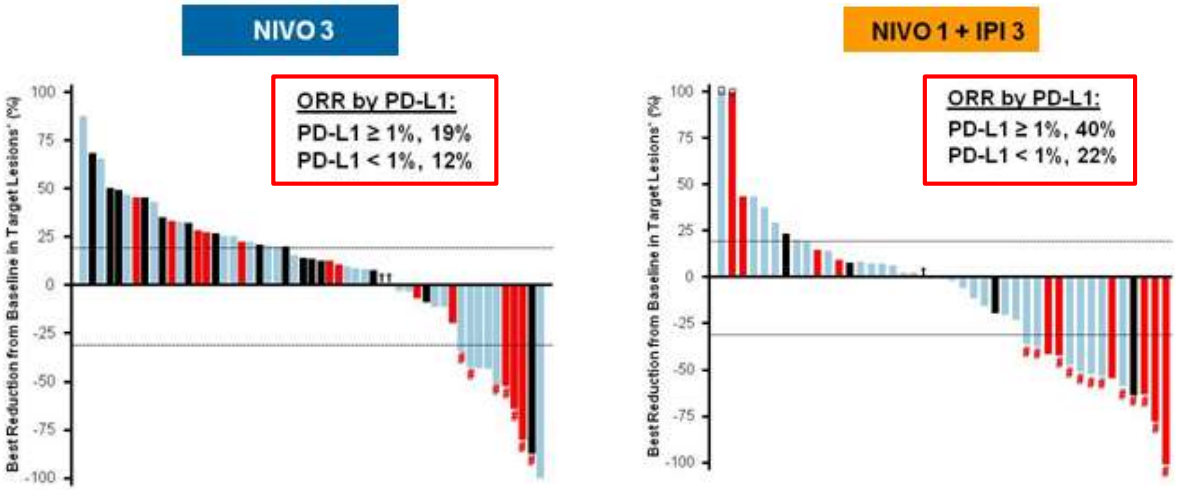
Educação e Pesquisa

Janjigian Y et al. *ASCO* 2017; Le D et al. *ASCO GI* 2016

CHECKMATE-032: resposta global (ORR)

	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
ORR, n (%)*	**7 (12)**	**12 (24)**	**4 (8)**
[95% CI]	[5, 23]	[13, 39]	[2, 19]
BOR, n (%)*			
Complete response	1 (2)	1 (2)	0
Partial response	6 (10)	11 (22)	4 (8)
Stable disease	12 (20)	8 (16)	15 (29)
Progressive disease	34 (58)	23 (47)	24 (46)
Not evaluable	6 (10)	6 (12)	9 (17)
DCR, n (%)†	19 (32)	20 (41)	19 (37)
Median TTR (range), months	1.6 (1.2 to 4.0)	2.7 (1.2 to 14.5)	2.6 (1.3 to 2.8)
Median DOR (95% CI), months	7.1 (3.0, 13.2)	7.9 (2.8, NE)	NR (2.5, NE)

- ✓ Maior resposta nos PD-L1 positivos
- ✓ **Houve resposta independentemente do status do PD-L1**



Janjigian Y et al. *ASCO* 2017; Le D et al. *ASCO GI* 2016

CHECKMATE-032: resposta global e controle de doença de acordo com MSI-H

- ✓ MSI-H em 15% dos pacientes: 11 dos 72 tumores avaliáveis
- ✓ MSI-H: maior RG (também houve resposta nos não-MSI-H)
- ✓ Amostra muito pequena

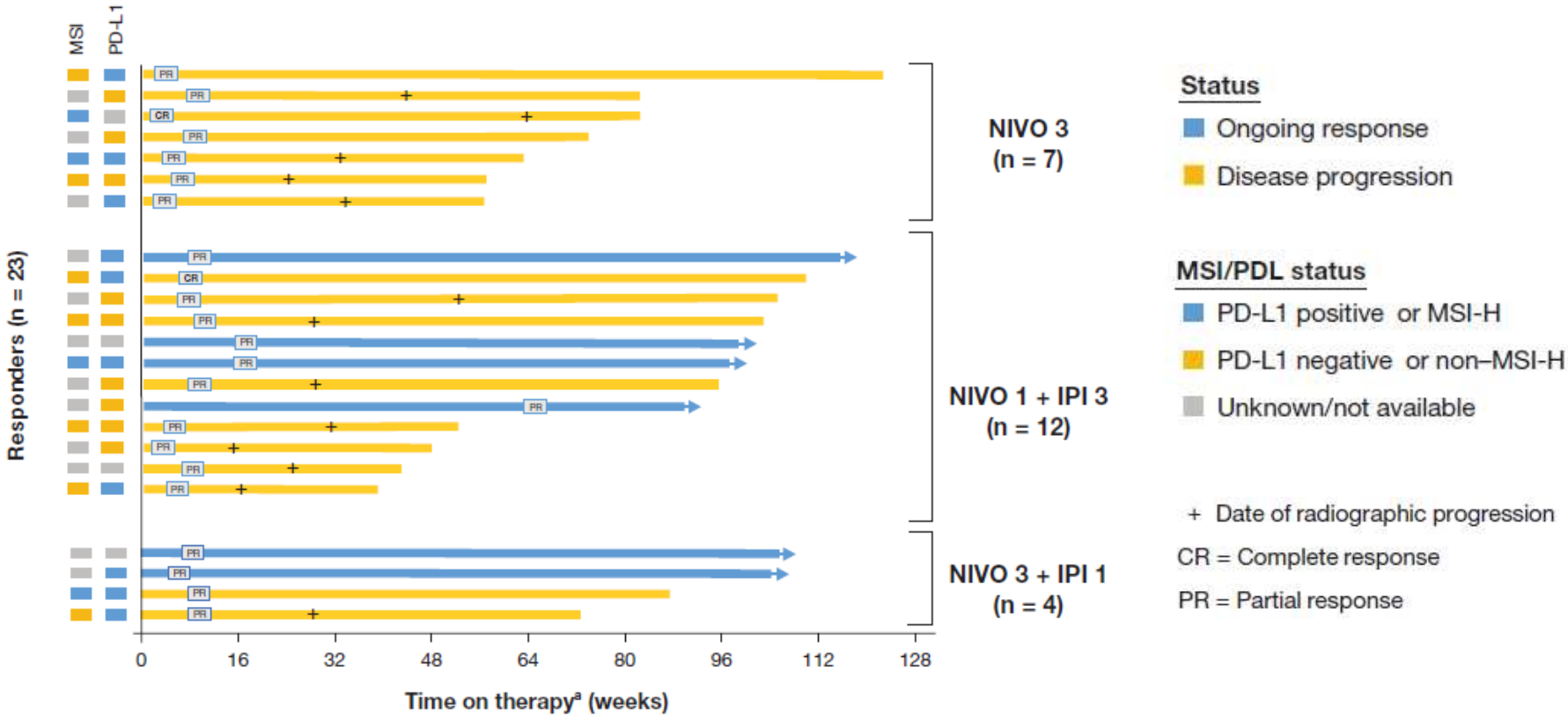
	NIVO 3 (n = 59)			NIVO 1 + IPI 3 (n = 49)			NIVO 3 + IPI 1 (n = 52)		
	MSI-H (n = 7)	Non–MSI-H (n = 18)	MSI-U (n = 34)	MSI-H (n = 2)	Non–MSI-H (n = 21)	MSI-U (n = 26)	MSI-H (n = 2)	Non–MSI-H (n = 22)	MSI-U (n = 28)
ORR, n (%)[a] [95% CI]	2 (29) [4, 71]	2 (11) [1, 35]	3 (9) [2, 24]	1 (50) [1, 99]	4 (19) [5,42]	7 (27) [12, 48]	1 (50) [1, 99]	1 (5) [0.1, 23]	2 (7) [0.9, 24]
BOR, n (%)[a]									
Complete response	1 (14)	0	0	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Partial response	1 (14)	2 (11)	3 (9)	1 (50)	3 (14)	7 (27)	1 (50)	1 (5)	2 (7)
Stable disease	3 (43)	3 (17)	6 (18)	0 (0)	5 (24)	3 (12)	0 (0)	7 (32)	8 (29)
Progressive disease	2 (29)	11 (61)	21 (62)	1 (50)	10 (48)	12 (46)	0 (0)	10 (45)	14 (50)
Not evaluable	0	2 (11)	4 (12)	0 (0)	2 (10)	4 (15)	1 (50)	4 (18)	4 (14)
DCR, n (%)[b]	5 (71)	5 (28)	9 (26)	1 (50)	9 (43)	10 (38)	1 (50)	8 (36)	10 (36)
Median TTR (range), months	1 (1, 2)	2 (1, 3)	3 (1, 4)	4 (4, 4)	3 (2, 3)	3 (1, 14)	3 (3, 3)	3 (3, 3)	2 (1, 3)
Median DOR (95% CI), months	10 (7, 13)	NR (3, NE)	7 (6, 13)	NR (NE, NE)	5 (3, NE)	10 (3, NE)	NR (NE, NE)	3 (NE, NE)	NR (NE, NE)

Educação e Pesquisa

Ott P et al. *ESMO 2017 (pôster 674P)*

CHECKMATE-032: Nivolumabe +/- Ipilimumabe podem levar a resposta duráveis em MSI-H ou não-MSI-H

- ✓ Respostas duráveis também foram observadas nos não-MSI-H e nos PD-L1 negativos
- ✓ Dos 23 respondedores todos 6 "*on-going*" possuem MSI-H ou PD-L1 positivo

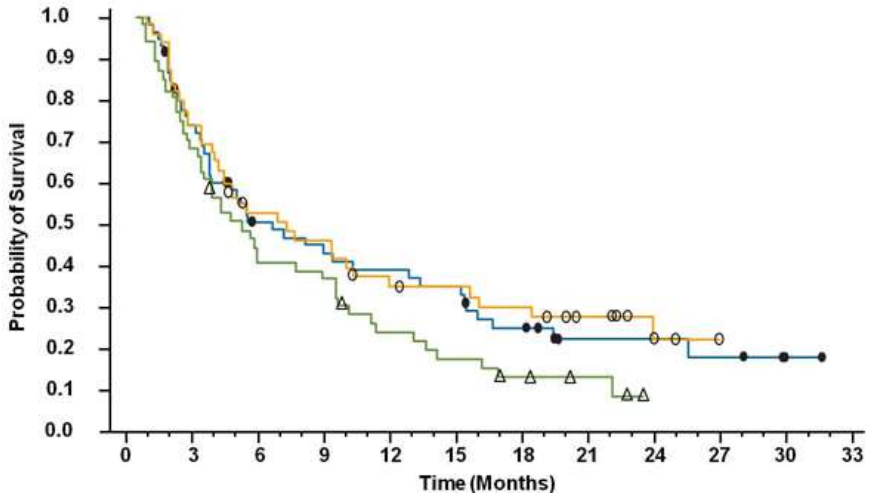


Educação e Pesquisa

Ott P et al. *ESMO 2017 (pôster 674P)*

CHECKMATE-032: SG por braço e status do PD-L1

- ✓ O benefício em SG com Nivolumabe ± Ipilimumabe foi **independente do PD-L1 e MSI-H**
- ✓ Atividade clínica e SG em pacientes com doença quimiorefratária são encorajadores



OS rate (95% CI), %	NIVO 3	NIVO 1 + IPI 3	NIVO 3 + IPI 1
Patients with PD-L1 ≥1%	n = 16	n =10	n = 13
12 months	34 (12, 57)	50 (18, 75)	23 (6, 47)
Patients with PD-L1 <1%	n = 26	n = 32	n = 30
12 months	45 (25, 6)	32 (16, 48)	25 (11, 42)

	mOS (95% CI), months	12-month OS rate, %	18-month OS rate, %
NIVO 3	6.2 (3.4, 12.4)	39	25
NIVO 1 + IPI 3	6.9 (3.7, 11.5)	35	28
NIVO 3 + IPI 1	4.8 (3.0, 8.4)	24	13

	NIVO 3 (n = 59)			NIVO 1 + IPI 3 (n = 49)		
	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)
Median OS, months [95% CI]	15 [2, NE]	6 [3, 12]	5 [3, 16]	NR [1, NE]	9 [4, 23]	4 [2, 16]
OS rate, % [95% CI]						
12 months	57 [17, 84]	33 [14, 55]	39 [22, 56]	50 [1, 91]	36 [16, 56]	33 [16, 51]
18 months	29 [4, 61]	17 [4, 37]	31 [15, 48]	50 [1, 91]	30 [12, 51]	24 [9, 42]

Educação e Pesquisa

Janjigian Y et al. *ASCO* 2017; Le D et al. *ASCO GI* 2016; Ott P et al. *ESMO 2017 (poster 674P)*

CHECKMATE-032: subgrupo em ≥ 2 linhas de QT

Nivolumab monotherapy in patients with advanced gastric or gastroesophageal junction (GEJ) cancer and 2 or more prior treatment regimens: Sub-analysis of the CheckMate 032 study

- ✓ Análise de eficácia em pacientes com as mesmas características do ATTRACTION-2
- ✓ **SG mediana: 8,5m** (95% CI, 3.35-15.01)
- ✓ **SG aos 12 meses: 44.3%**

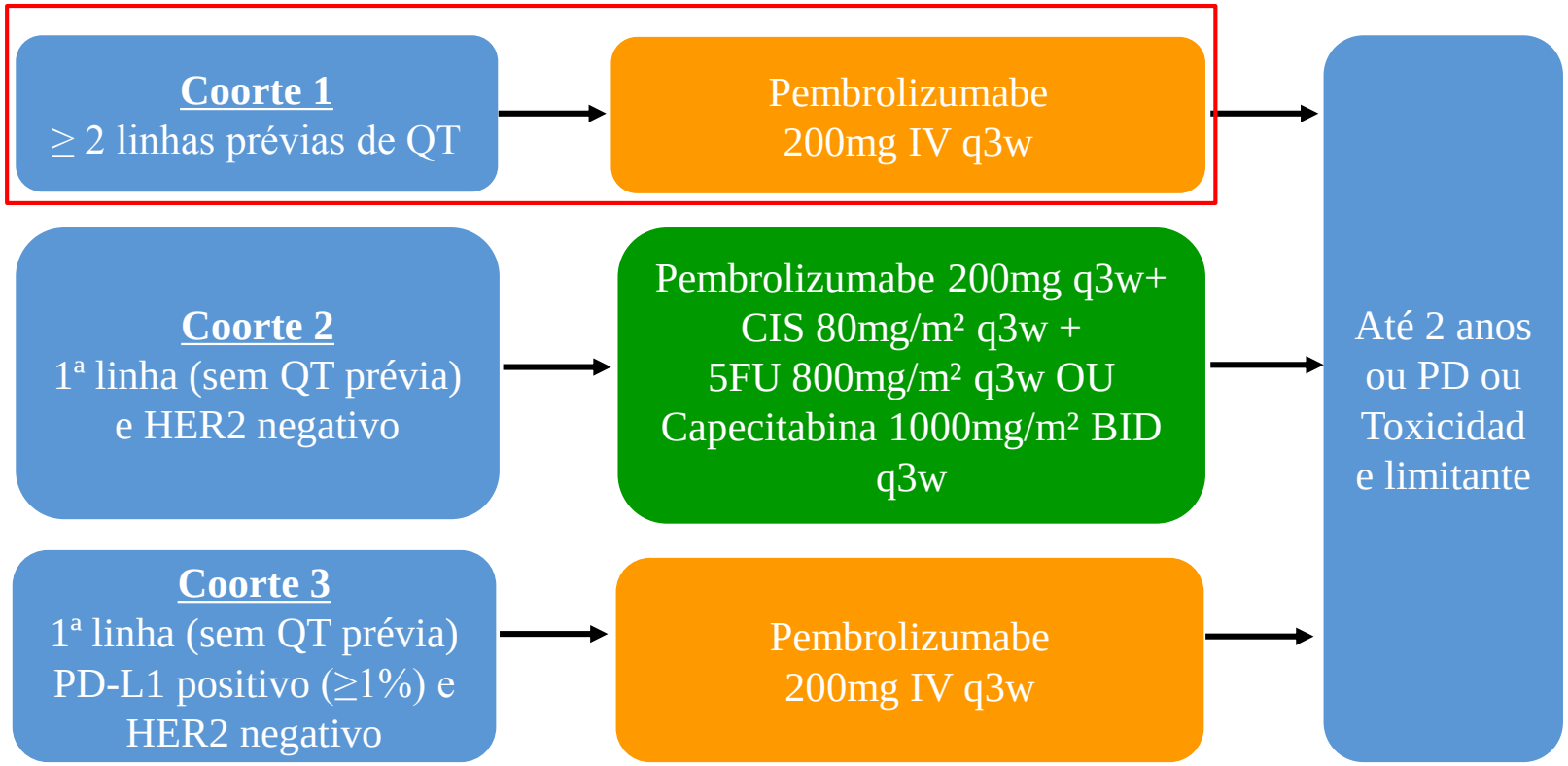
Table: BOR, TTR, and DOR per BICR and INV.

	Nivolumab 3 mg/kg n=42	
	BICR	INV
ORR, n (%)	3 (7.1)	7 (16.7)
BOR, n (%)		
CR	0	2 (4.8)
PR	3 (7.1)	5 (11.9)
SD	13 (31.0)	7 (16.7)
PD	16 (38.1)	23 (54.8)
Unknown	10 (23.8)	5 (11.9)
DCR, n (%)	16 (38.1)	14 (33.3)
TTR, median (range), months	1.38 (1.2-1.4)	1.51 (1.2-4.0)
DOR, median (95% CI), months	NA (2.83-NA)	6.97 (2.96-NA)

Educação e Pesquisa

Patrick Ott et al. *ESMO GI* 2017 (pôster O-007)

KEYNOTE-059: Fase II multicoorte não-randomizado de Pembrolizumabe em GC/GEJ Adenocarcinoma



Fuchs CS et al. *ASCO* 2017 (abstr 4003)

KEYNOTE-059 (coorte 1): resposta objetiva

	All Patients N = 259		PD-L1 Positive[a] n = 148		PD-L1 Negative n = 109	
Response[b]	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
ORR	**12**	**8-17**	**16**	**11-23**	**6**	**3-13**
DCR[c]	27	22-33	34	26-42	19	12-28
BOR						
CR	3	1-6	3	1-8	3	1-8
PR	9	6-13	13	8-19	4	1-9
SD	16	12-21	18	12-25	15	9-23
PD	56	49-62	53	44-61	60	50-69

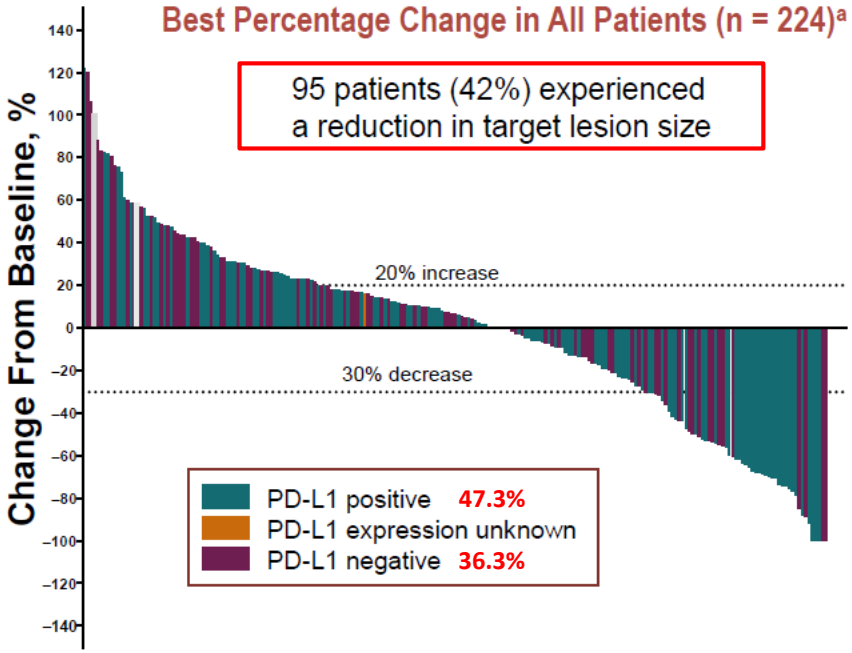
- Median (range) follow-up in cohort 1: 5.6 (0.5-24.7) months
- 134 patients received pembrolizumab as third-line therapy; ORR was 16%, and DCR was 31%
- 125 patients received pembrolizumab as fourth plus–line therapy; ORR was 7%, and DCR was 23%

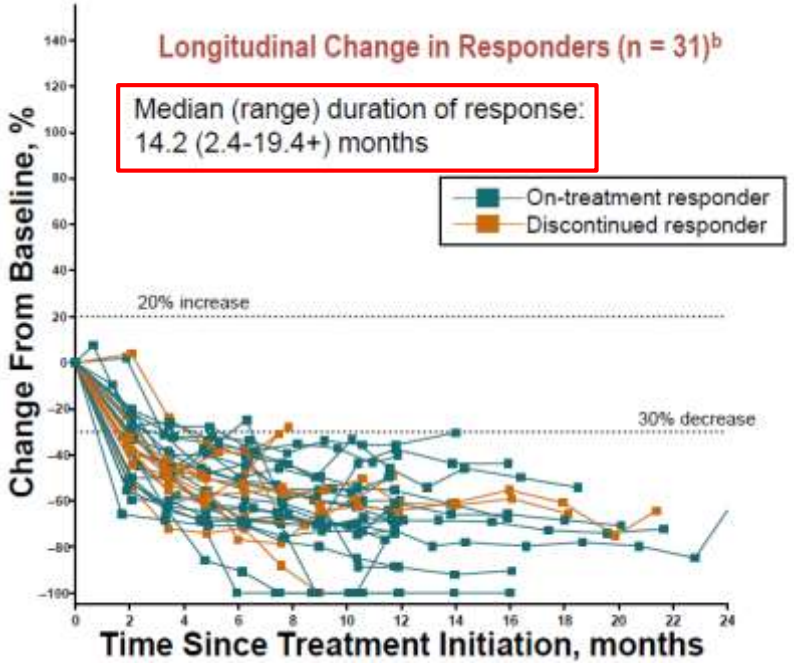
MSI-H (4%): ORR 57.1%

Educação e Pesquisa

Wainberg ZA et al. *ESMO* 2017 (abstr LBA28_PR)

KEYNOTE-059 (coorte 1): redução tumoral e duração de resposta (DoR)



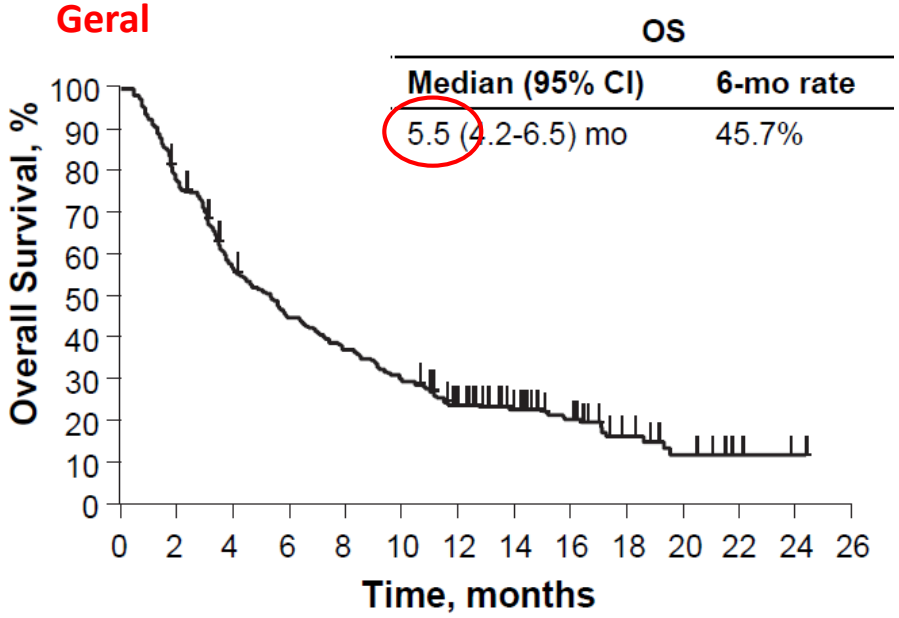


PD-L1 positivie: 16.3 mo
PD-L1 negative: 6.9 mo

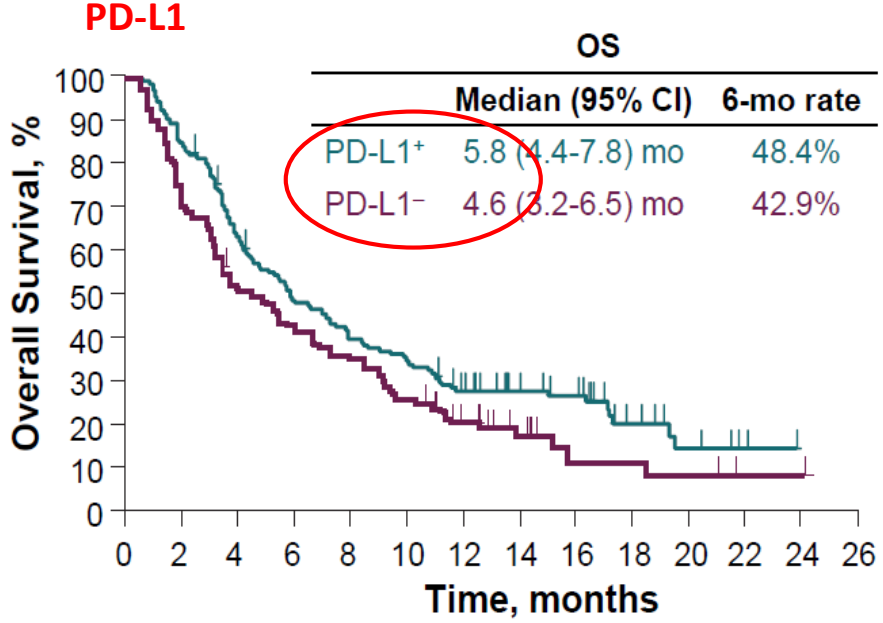
Wainberg ZA et al. *ESMO* 2017 (abstr LBA28_PR)

KEYNOTE-059 (coorte 1): SG na população geral e pelo status PD-L1

Geral



PD-L1



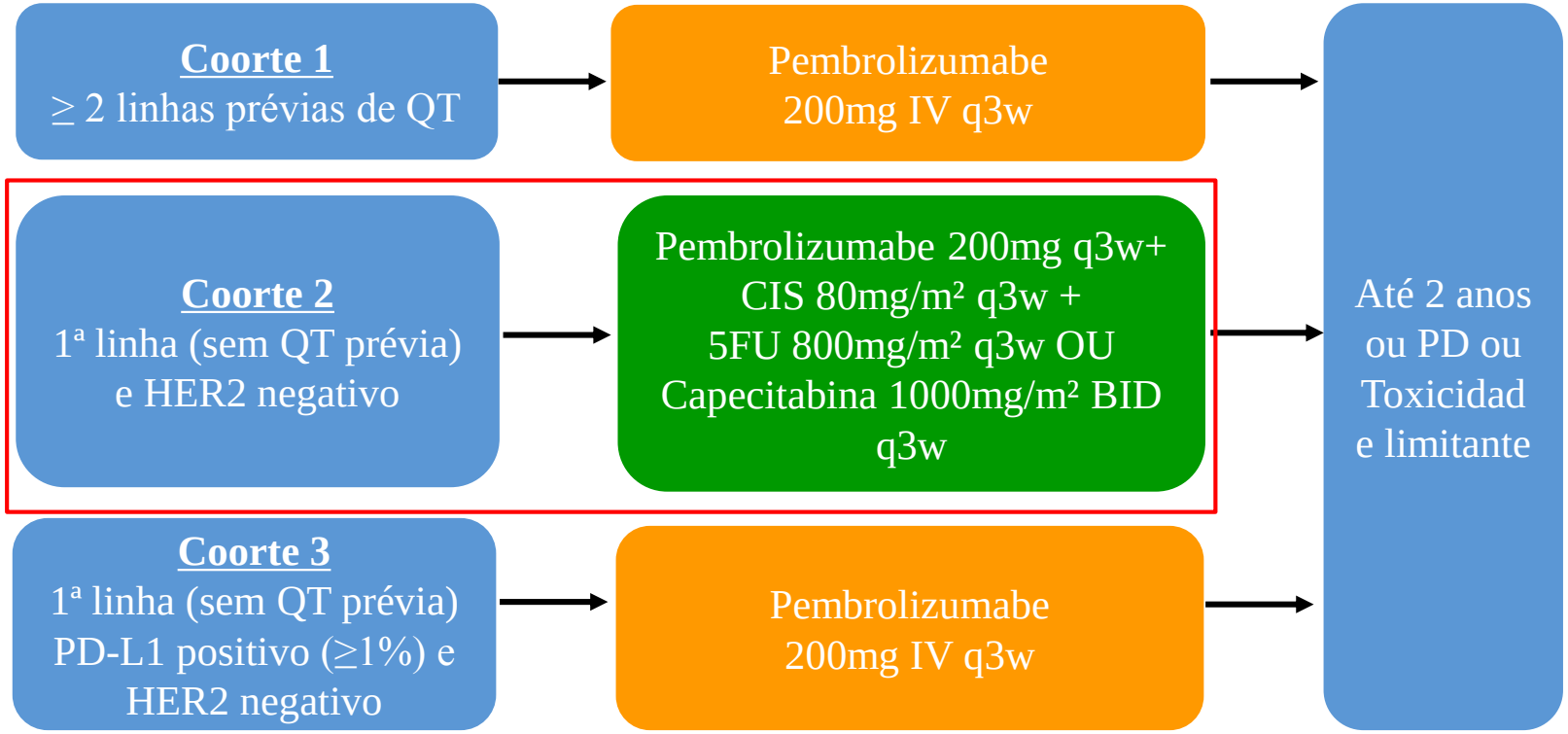
FDA grants accelerated approval to pembrolizumab for advanced gastric cancer

On September 22, 2017, the Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for patients with recurrent locally advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 as determined by an FDA-approved test. Patients must have had disease progression on or after two or more prior systemic therapies, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy.

Educação e Pesquisa

Wainberg ZA et al. *ESMO* 2017 (abstr LBA28_PR)

KEYNOTE-059: Fase II multicoorte não-randomizado de Pembrolizumabe em GC/GEJ Adenocarcinoma

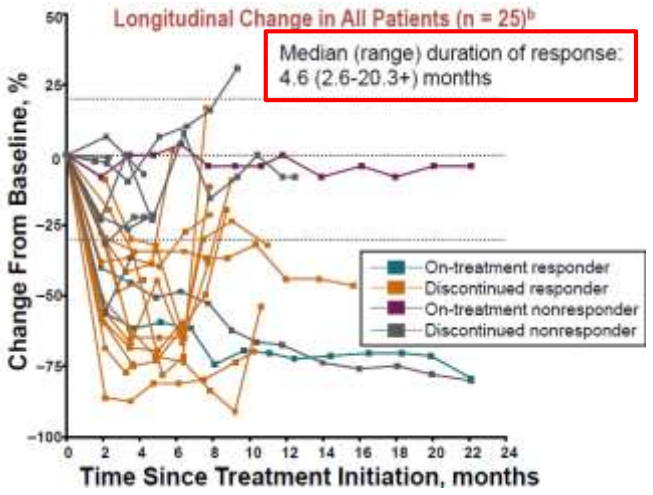


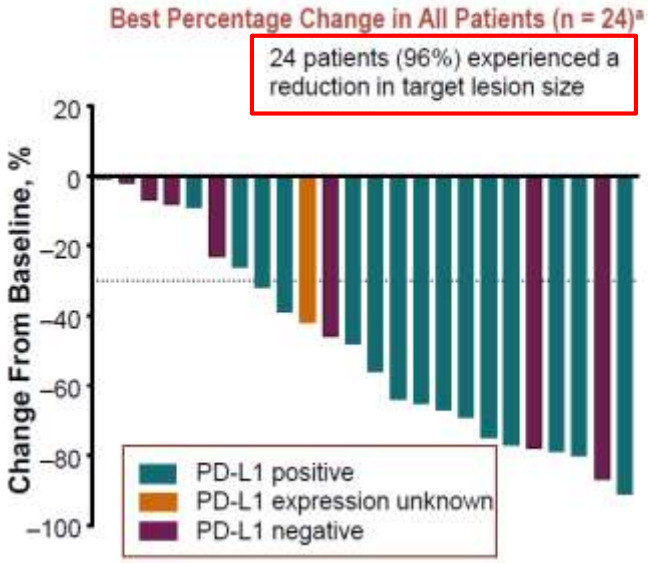
Bang YJ et al. *ASCO* 2017 (abstr 4012)

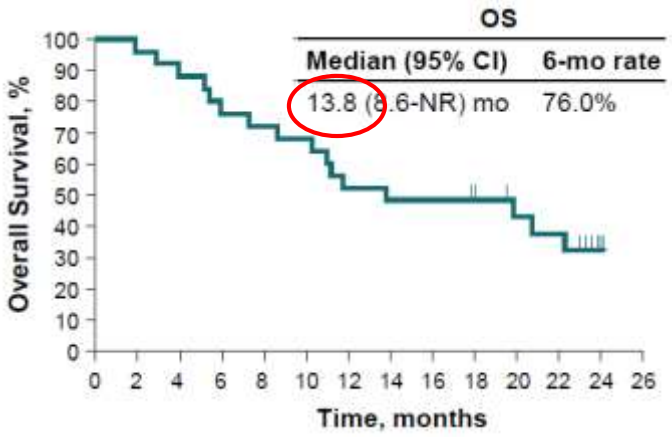
KEYNOTE-059: (coorte 2): resposta objetiva, DoR e SG

Coorte muito pequena!

	All Patients N = 25		PD-L1 Positive[a] n = 16		PD-L1 Negative n = 8	
Response[b]	%	95% CI	%	95% CI	%	95% CI
ORR	60	39-79	69	41-89	38	9-76

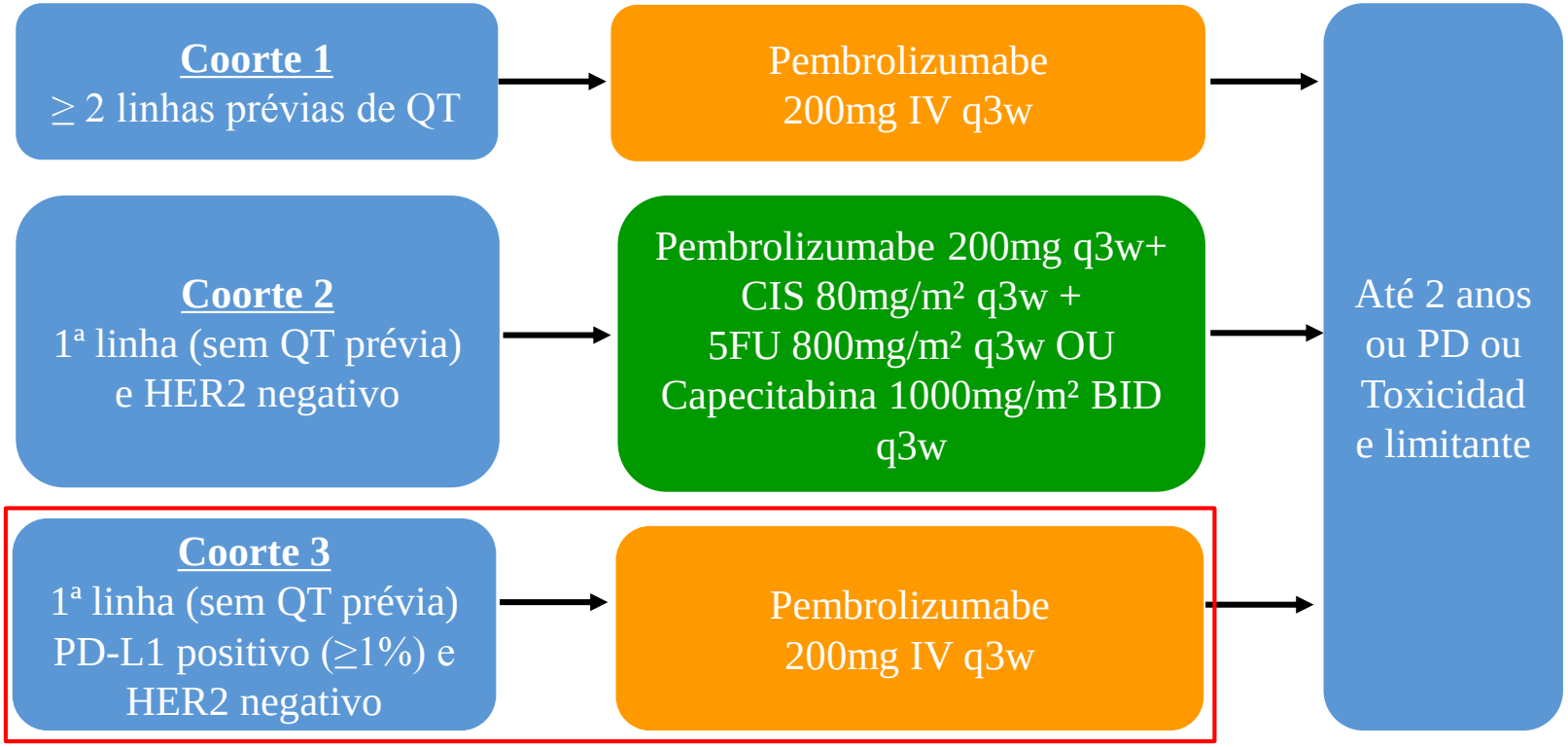






Wainberg ZA et al. *ESMO* 2017 (abstr LBA28_PR)

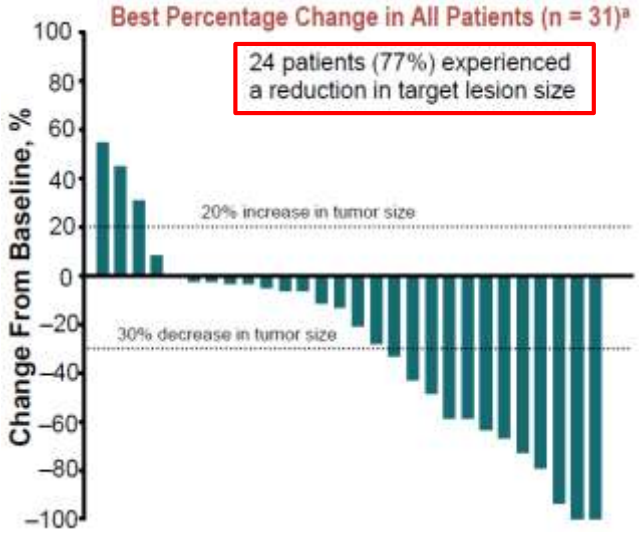
KEYNOTE-059: Fase II multicoorte não-randomizado de Pembrolizumabe em GC/GEJ Adenocarcinoma

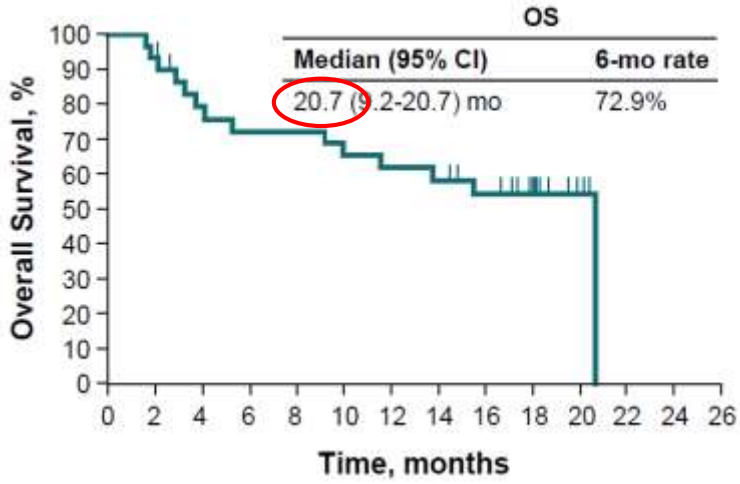


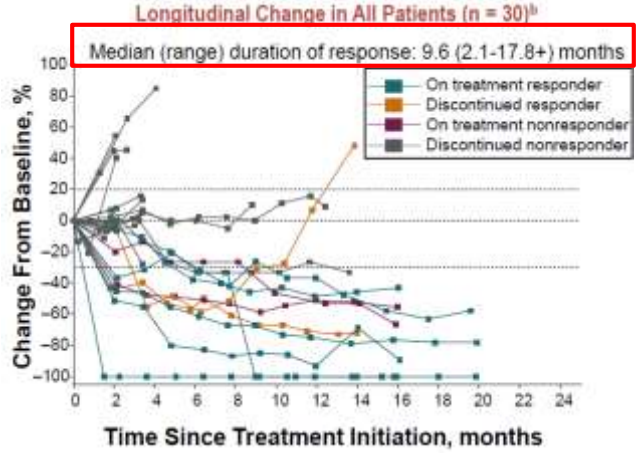
Catenaci D et al. *ESMO GI* 2017

KEYNOTE-059 (coorte3): eficácia

	N = 31	
Response[a]	%	95% CI
ORR	26	12-45







Educação e Pesquisa

Wainberg ZA et al. *ESMO* 2017 (abstr LBA28_PR)

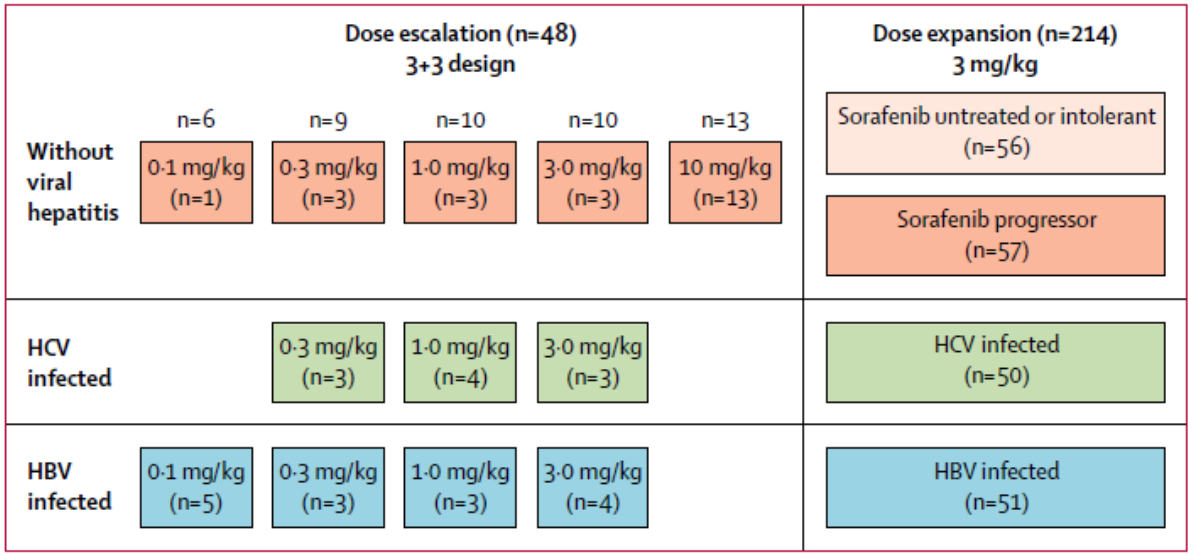
Câncer de Estômago: estudos em andamento com Inibidores de Checkpoint

Trial	Fase	Linha	N	Tratamento
KEYNOTE-062	III	1ª, HER2 negativo PD-L1 +	750	**Pembrolizumabe** isolado ou Pembrolizumabe + QT ou QT isolada
KEYNOTE-061	III	2ª	720	**Pembrolizumabe** vs Paclitaxel
CHEKMATE 577	III	Adjuvante (pós-QTRT)	760	**Nivolumabe** ou Placebo
CHEKMATE 649	III	1ª, HER2 negativo	1266	**Nivolumabe + Ipilimumabe** ou Nivolumabe + QT ou QT isolada
JAVELIN 100	III	Manutenção pós-1ª	666	QT por 12 semanas seguido de **Avelumabe** ou continuar QT
JAVELIN 300	III	3ª	330	**Avelumabe** + BSC ou Paclitaxel/Irinotecano + BSC

Hepatocarcinoma

CHECKMATE-040: desenho do estudo

- ✓ **Fase 1/2**, aberto, braço único, n=262: fase de escalonamento da dose (n=48) e **fase de expansão (n=214)**
- ✓ HCC irressecável, BCLC B/C, Child-Pugh ≤ 7 (até B7), **independente do PD-L1**
- ✓ **HBV**: necessário terapia antiviral prévia (carga viral <100IU/mL); **HCV** não necessário
- ✓ **Maioria (68%) após falha ao Sorafenibe** e com metástase extra-hepática (67%)
- ✓ Fase de expansão: **nivolumabe** 3 mg/kg q2w até PD ou toxicidade limitante



Study Endpoints

Primary
- Safety and tolerability (ESC)
- ORR (EXP)[a]

Secondary
- ORR (ESC)[a]
- Disease control rate
- Time to response
- Duration of response
- Overall survival

Educação e Pesquisa

Crocenzi T et al. *ASCO* 2017; El-Koueiry AB et al. *Lancet* 2017;389:2492-2502

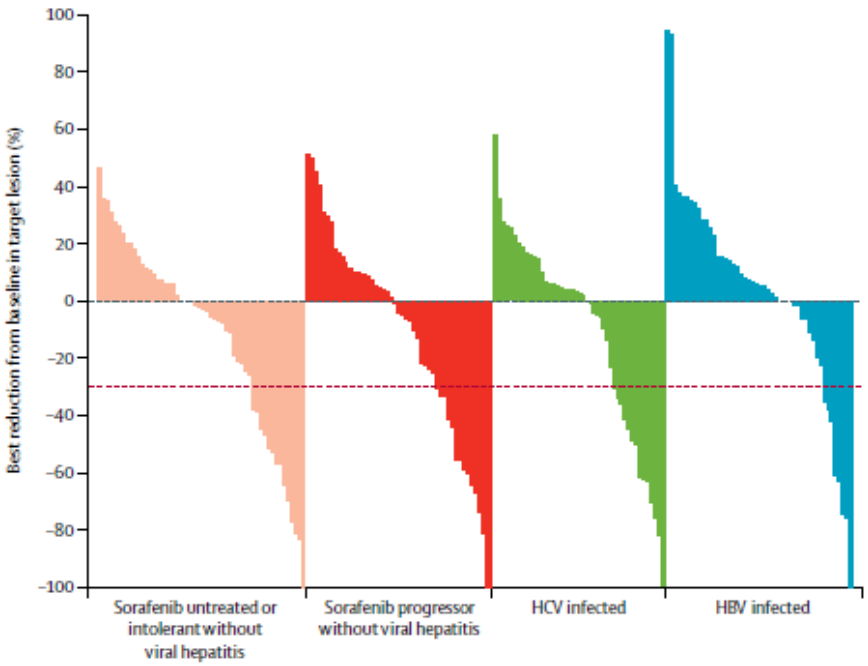
CHECKMATE-040: eficácia

	Escalonamento de Dose (n=48)	Expansão (n = 214)
Resposta objetiva	15% (7/48)	**20%** (42/214); Destes 67% (28/42) ***ongoing***
Controle de doença (DCR)		**64%**
Resposta precoce (<3 meses)	71% (5/7)	69% (29/42)
Descontinuidade por Toxicidade	6% (3/48)	4% (8/214)
Mediana de Duração de Resposta	17 meses	**9,9 meses**
Mediana de Tempo para PD	3,4 meses	4,1 meses
Mediana de SG	15 meses	**13,2 meses / NR**
SG em 9 meses	66%	**74%**

Educação e Pesquisa

El-Koueiry AB et al. *Lancet* 2017;389:2492-2502

CHECKMATE-040: eficácica



- ✓ **Resposta independe** do status de uso de Sorafenibe, da etiologia (virus B ou C) e **do status do PD-L1**
- ✓ **PD-L1+ em 20%** (34/174)
- ✓ **RG em PD-L1 positivo:** 26% (9/34)
- ✓ **RG em PD-L1 negativo**: 19% (26/140)

CHECKMATE-459 (on going): fase 3
Nivolumabe vs Sorafenibe na 1ª linha

FDA grants accelerated approval to nivolumab for HCC previously treated with sorafenib

On September 22, 2017, the Food and Drug Administration granted accelerated approval to nivolumab (OPDIVO, Bristol-Myers Squibb Co.) for the treatment of hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib.

Educação e Pesquisa

El-Koueiry AB et al. *Lancet* 2017;389:2492-2502

Hepatocarcinoma: Durvalumabe (anti-PD-L1) +/- Tremelimumabe (anti-CTLA4)

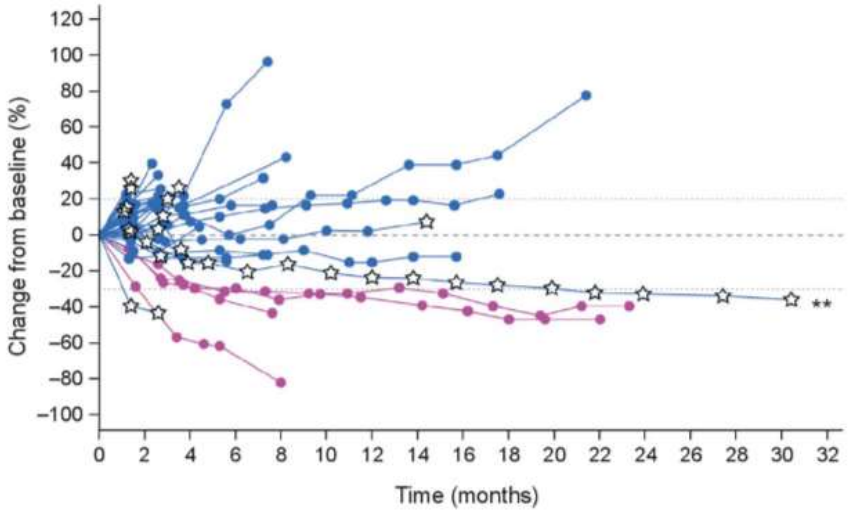
- ✓ **Fase 1/2**, aberto de braço único, em tumores sólidos, análise da coorte de HCC
- ✓ Durvalumabe 10mg/Kg IV q2w por 1 ano ou PD ou toxicidade
- ✓ Estudo da combinação: Durvalumabe 20mg/Kg + Tremelimumabe 1mg/Kg, ambos q4w por 4 doses, seguido de Durva 20mg/Kg q4w até PD ou toxicidade
- ✓ HBV: necessário terapia antiviral prévia (carga viral <100IU/mL); HCV não necessário
- ✓ Independente do PD-L1

	Durvalumab n=39	Durvalumab + Tremelimumab n=40	Nivolumab n=262
HCC	Child-Pugh A	Child-Pugh < B7	Child-Pugh ≤ 7
Pós-Sorafenibe	93%	75%	68%
End-point 1º	RG	segurança	RG e segurança
RG (CR+PR)	10%	**17.5%**	**20%**
Controle de doença (DCR)	32.5%	**57.6%**	**NR**
Mediana de SG	**13.2 meses**	NR	**13.2**
SG em 12 meses	**56.1%**	NR	NR

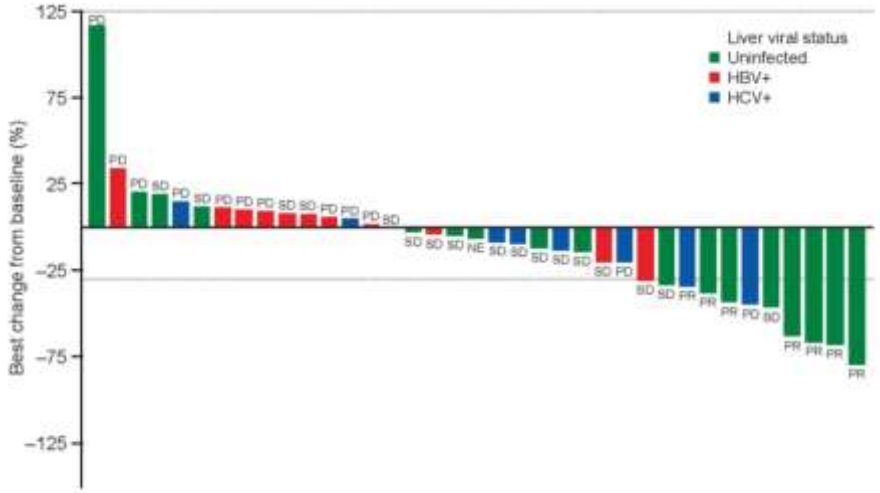
Educação e Pesquisa

Wainberg Z et al. *ASCO* 2017 (abstr 4071); Kelley RK et al. *ASCO* 2017 (abstr 4074)

Hepatocarcinoma: Durvalumabe (anti-PD-L1) +/- Tremelimumabe (anti-CTLA4)



Respostas precoces e duradouras



Maior atividade clínica em pacientes não-infectados, embora respostas foram observadas em HCV+ e HBV+

Educação e Pesquisa

Wainberg Z et al. *ASCO* 2017 (abstr 4071); Kelley RK et al. *ASCO* 2017 (abstr 4074)

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

For Immediate Release May 23, 2017

Release

The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

Keytruda (pembrolizumab) is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.

Take Home Message: imunoterapia em TGI alto

- ✓ As maiores evidências de IO são para os tumores gástricos
- ✓ Em sua maioria baseiam-se em estudos iniciais
- ✓ No geral, os dados em SG são imaturos (exceção: ATTRACTION-2)
- ✓ Estudos de fase 3 em cenários mais precoces já em andamento
- ✓ Necessidade urgente de padronização dos testes de PD-L1

  - PD-L1+ em câncer de estômago: 57% (KEYNOTE059) vs 31% (CHECKMATE032)

- ✓ Tendência à maior atividade em PD-L1 positivo
- ✓ Entretanto, em câncer de estômago e HCC, o benefício independe do status do PD-L1

Take Home Message: imunoterapia em TGI alto

✓ MSI-H (4%) parece ser um bom biomarcador: maior RG

- KEYNOTE-059: 57% x 9% com Pembrolizumabe

- CHECKMATE-32: 29% x 11% com nivolumabe (50% x 19% N1+I3)

✓ Além do PD-L1 e MSI: score de perfil gênico? Tumor burden?

✓ Qual o papel da combinação de anti-PD-1/PD-L1 (com QT ou anti-CTLA4): parece aumentar a RG, mas qual o impacto em SG?

✓ Para um uso mais custo-efetivo é necessário uma adequada seleção dos pacientes (e para isso é fundamental uma melhor compreensão sobre os biomarcadores)


IV Simpósio Internacional de Tumores Gastrointestinais
16 e 17 • março • 2018
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