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IMMUNOTHERAPY IN METASTATIC GASTRIC CANCER

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DISCLAIMER

Please note:

The views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author's academic institution or the rest of the GI CONNECT group.

Disclosures:

- Dr. Dotan has the following financial disclosures:
  - Research Grant support paid to institution from Lilly and Pfizer
  - Honorarium from Boston Medical and Pfizer
  - Clinical trial funding to institution from: AstraZeneca, Merck, Incyte, Boston Medical, GSK, Medimmune

CHECKPOINT INHIBITORS IN THE 3RD-LINE SETTING

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KEYNOTE-059[1,2]: (NCT02335411)

- Phase II, 3 single-arm cohorts
- Cohort 1 – Nth-line therapy with pembrolizumab 200 mg q3w
- N=259 patients
- PD-L1+ /-
- Primary end point ORR and safety

ATTRACTION-2[3]: (NCT02267343)

- Phase III, Asian study
- Patients with advanced gastric or gastro-oeasophageal junction cancer with at least 2 prior therapies
- Patients randomized between nivolumab 3 mg/kg q2w (n=330) and placebo (n=163)
- PD-L1 agnostic
- Primary endpoint OS

Nth-line, 3rd-line or beyond; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; q2w, every 2 weeks; q3w, every 3 weeks.

1. Fuchs CS, et al. JAMA Oncol. 2018;4(5):e180013; 2. Wainberg ZA, et al. 2019 ASCO Annual Meeting abstract 4009;
3. Kang Y-K, et al. Lancet. 2017;390(10111):2461-71.

CHECKPOINT INHIBITORS APPROVED IN 3RD-LINE GASTRIC CANCER

	KEYNOTE-059[1,2] (Pembrolizumab 200 mg q3w)		ATTRACTION-2[3] (Nivolumab 3 mg/kg q2w)
	PD-L1+ CPS >1 (N=148)	**PD-L1- (N=109)**	**PD-L1 agnostic (N=268)**
Objective response	**15.5%**	**6.4%**	**11%**
Complete response	2.0%	2.8%	0
Partial response	13.5%	3.7%	11%
Stable Disease	17.6%	14.7%	29%
Disease control	**33.1%**	**19.3%**	**40%**
Duration of response, median	16.3 mo	6.9 mo	9.53 mo
Median PFS	**2.0 months**		**1.61 months**
Median OS	**5.6 months**		**5.26 months**
12-month OS	26.2%	15.1%	26.2%
24-month OS	20.2%	9.2%	

CPS, combined positive score; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; q2w, every 2 weeks; q3w, every 3 weeks.

1. Fuchs CS, et al. JAMA Oncol. 2018;4(5):e180013; 2. Wainberg ZA, et al. 2019 ASCO Annual Meeting abstract 4009;
3. Kang Y-K, et al. Lancet. 2017;390(10111):2461-71.

JAVELIN GASTRIC 300: AVELUMAB VS CHEMOTHERAPY IN THE 3RD-LINE SETTING

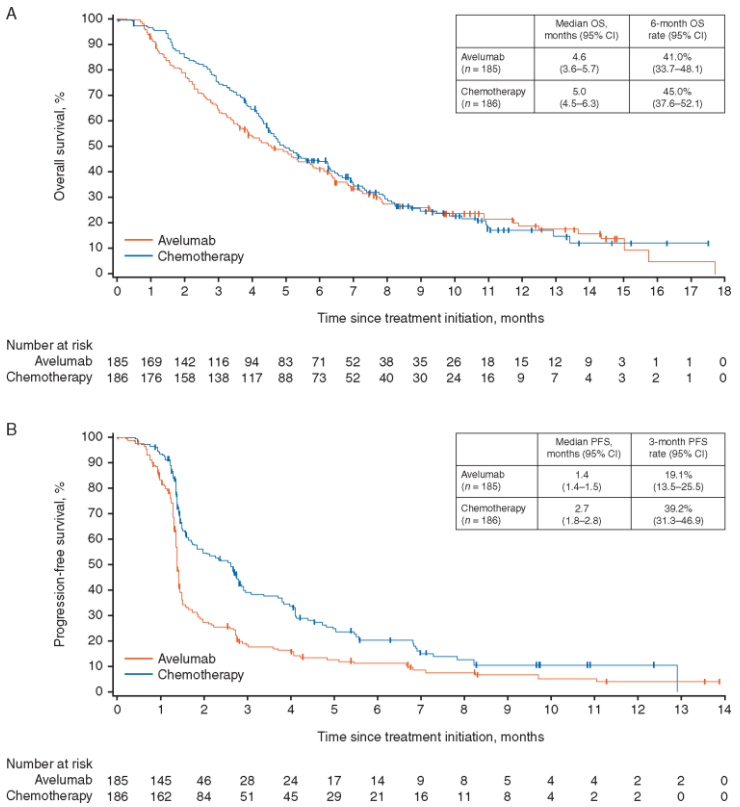
Phase 3, international, randomized controlled trial of avelumab vs. physician's choice chemotherapy (paclitaxel/irinotecan)

371 patients with advanced GC/GEJC who had received two prior lines of therapy were randomized

advanced GC/GEJC
Received 2 prior lines of therapy

- Avelumab 10 mg/kg q2w (n=185)
- Paclitaxel 80 mg/m^2 days 1, 8, and 15
  Or
  Irinotecan 150 mg/m^2 days 1 and 15
  (n=186)

	Med OS	Med PFS	ORR	DCR
Avelumab	4.6 mo	1.4 mo	2.2%	22.2%
Chemo	5.0 mo	2.7 mo	4.3%	44.1%



CI, confidence interval; DCR, disease control rate; GC/GEJC, gastric cancer/gastro-oesophageal junction cancer; Med, median; mGC, metastatic gastric cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q2w, every 2 weeks.

Bang YJ, et al. Ann Oncol. 2018;29(10):2052-60.

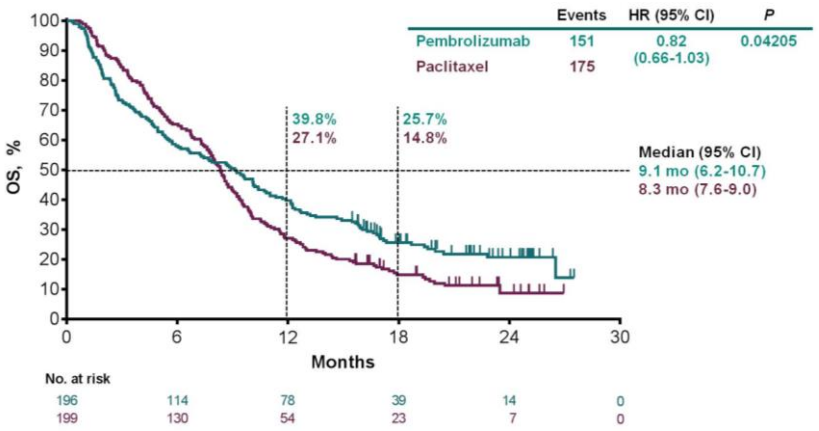
KEYNOTE-061: CHECKPOINT INHIBITORS IN THE 2ND-LINE SETTING

- GEJ/gastric adenocarcinoma
- Progressed on 1st-line platinum/fluoropyrimidine
- PD-L1+ (CPS ≥1)
- N=592 randomized (395 CPS ≥1)

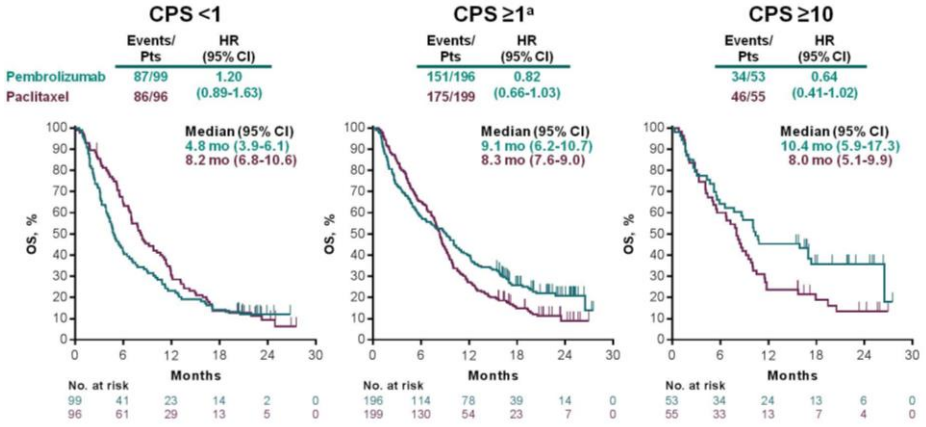
→ Pembrolizumab 200 mg q3w (up to 2 years) N=296 (196 CPS ≥1)

→ Paclitaxel 80 mg/m² days 1, 8, 15 of 4-week cycles N=296 (199 CPS ≥1)

Overall Survival: CPS ≥1



Overall Survival by PD-L1 CPS



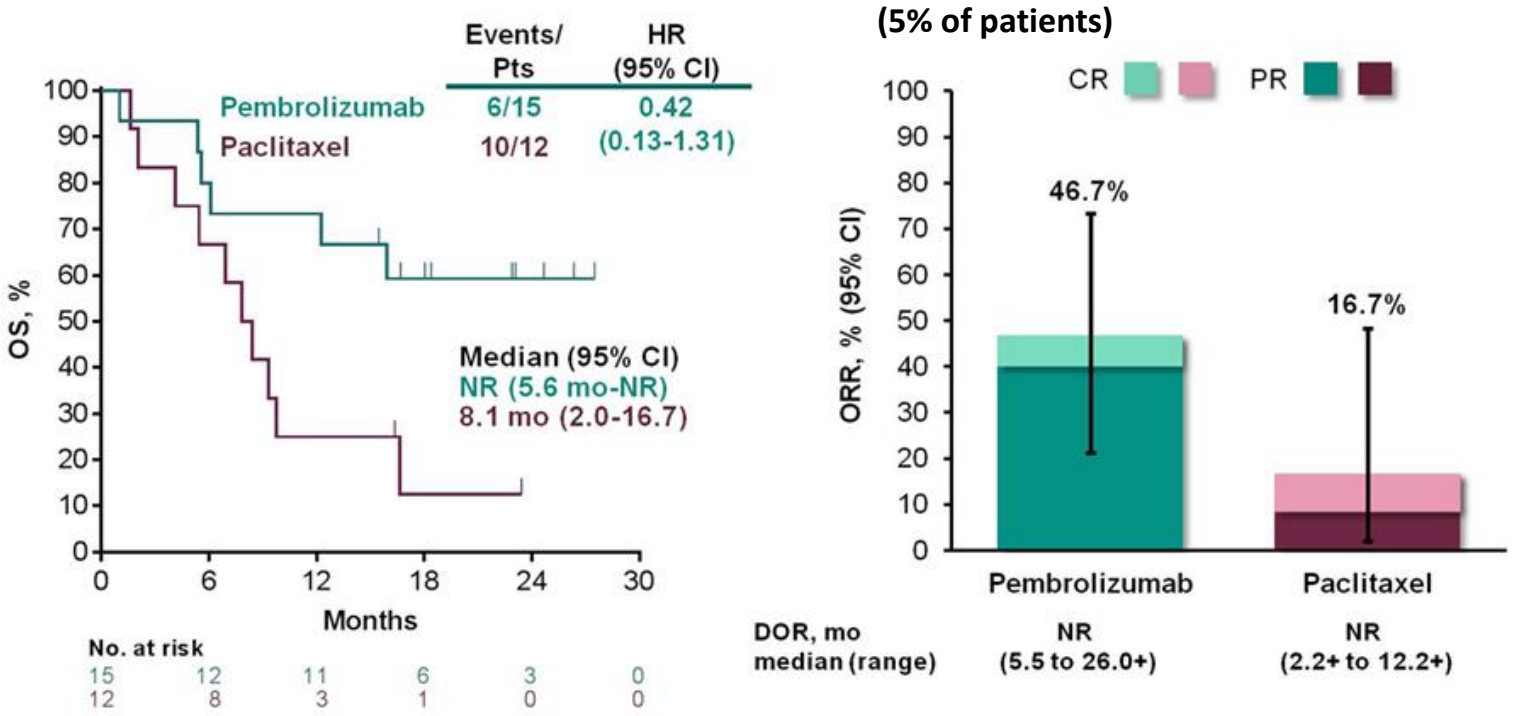
Data cutoff date: October 26, 2017. [a]Primary end point.

CI, confidence interval; CPS, combined positive score; GEJ, gastro-oesophageal junction; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1; q3w, every 3 weeks.

Fuchs CS, et al. 2018 ASCO Annual Meeting abstract 4062; Shitara K, et al. Lancet. 2018;392(10142):123-33.

KEYNOTE-061: CHECKPOINT INHIBITORS IN THE 2ND-LINE SETTING

OS, ORR, and DOR for MSI-H Tumors[a]



[a]Post-hoc subgroup analysis. Data cutoff date: October 26, 2017.

CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; MSI-H, microsatellite instability-high; NR, not reached; ORR, overall response rate; OS, overall survival; PR, partial response; Pts, patients.

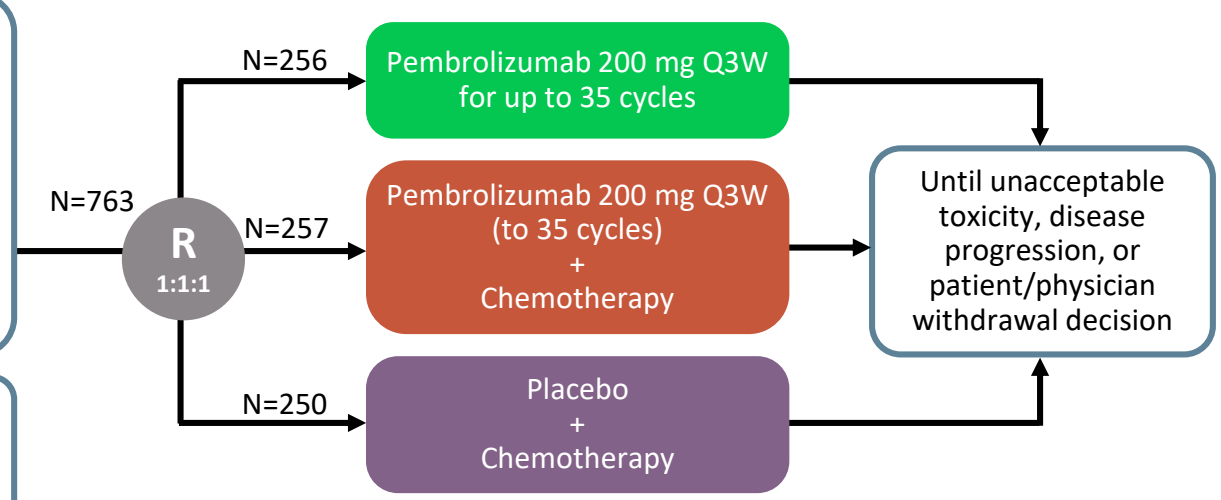
Presented by Kohei Shitara at 2018 ASCO Annual Meeting (Abstract 4062).

KEYNOTE-062: CHECKPOINT INHIBITORS IN THE 1ST-LINE SETTING

KEYNOTE-062 STUDY DESIGN (NCT02494583)

Key Eligibility Criteria
- Locally advanced, unresectable or metastatic gastric or gastroesophageal adenocarcinoma
- HER2/neu-negative, PD-L1-positive disease (CPS ≥1)
- ECOG PS 0 or 1

Stratification Factors
- Region
- Locally advanced or metastatic disease
- 5-FU or capecitabine



Primary endpoints: OS and PFS
Secondary endpoints: ORR, DOR, QoL

Events: N (%)	Pembro	P + C	Chemo
CPS ≥10	92 (36%)	99 (39%)	90 (36%)
MSI-H	14 (5%)	17 (7%)	19 (8%)
MSI-H + CPS ≥10	11 (79%)	11 (65%)	10 (53%)

5-FU, 5-fluorouracil; C, chemotherapy; Chemo, chemotherapy; CPS, combined positive score; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability-high; ORR, overall response rate; OS, overall survival; P, pembrolizumab; Pembro, pembrolizumab; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; QoL. Quality of life; R, randomization.

Presented by Josep Tabernero at 2019 ASCO Annual Meeting (Abstract LBA4007).

KEYNOTE-062: CHECKPOINT INHIBITORS IN THE 1ST-LINE SETTING

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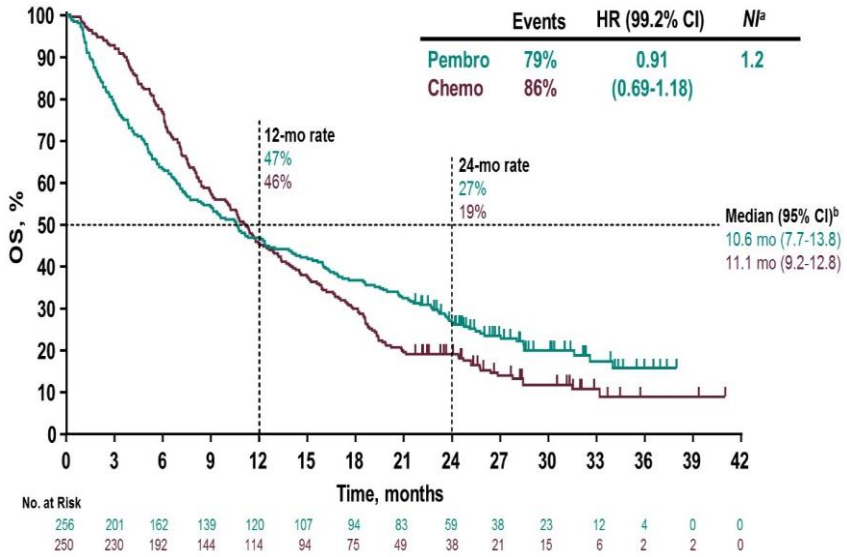
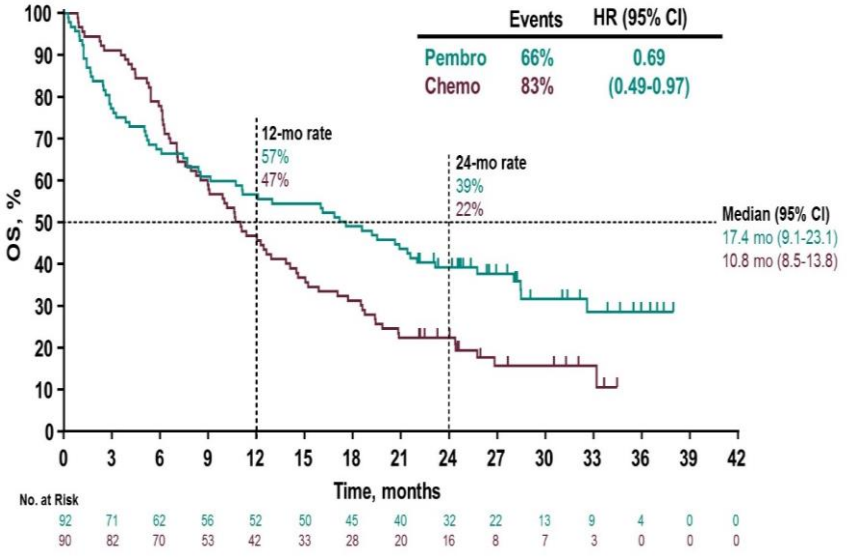
Overall Survival: P vs C (CPS ≥1)



Overall Survival: P vs C (CPS ≥10)



- Primary end point was met, pembrolizumab was non-inferior to chemotherapy for OS
- In CPS ≥10 – pembrolizumab is better than chemotherapy especially at 12 and 24 months
- There is initial drop in the first few months, highlighting the concern with IO therapy early on in the disease

[a]NI, non-inferiority margin; [b]HR (95% CI) = 0.91 (0.74–1.10), *P*=0.162 for superiority of P vs C. Data cutoff date: March 26, 2019.

C, chemotherapy; Chemo, chemotherapy; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; IO, immuno-oncology; NI, non-inferiority margin; OS, overall survival; P, pembrolizumab; Pembro, pembrolizumab.

Presented by Josep Tabernero at 2019 ASCO Annual Meeting (Abstract LBA4007).

KEYNOTE-062: CHECKPOINT INHIBITORS IN THE 1ST-LINE SETTING

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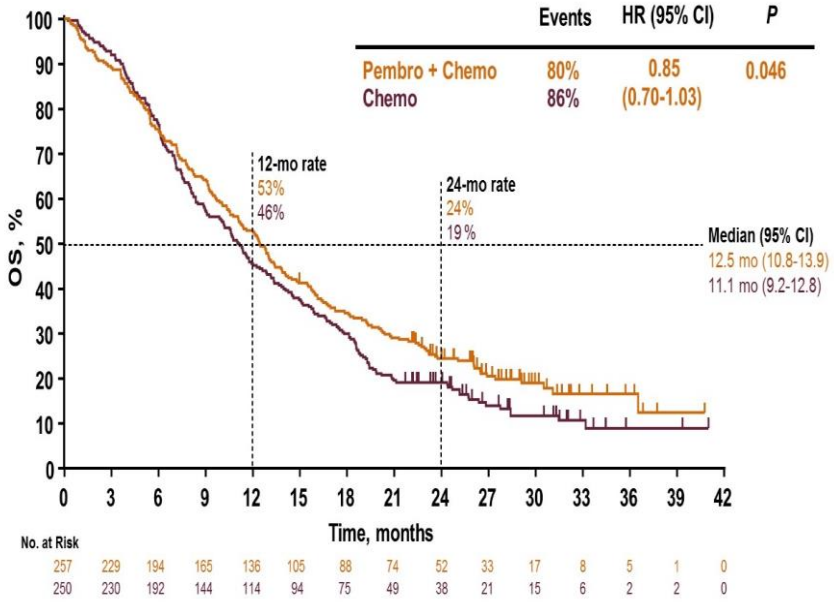
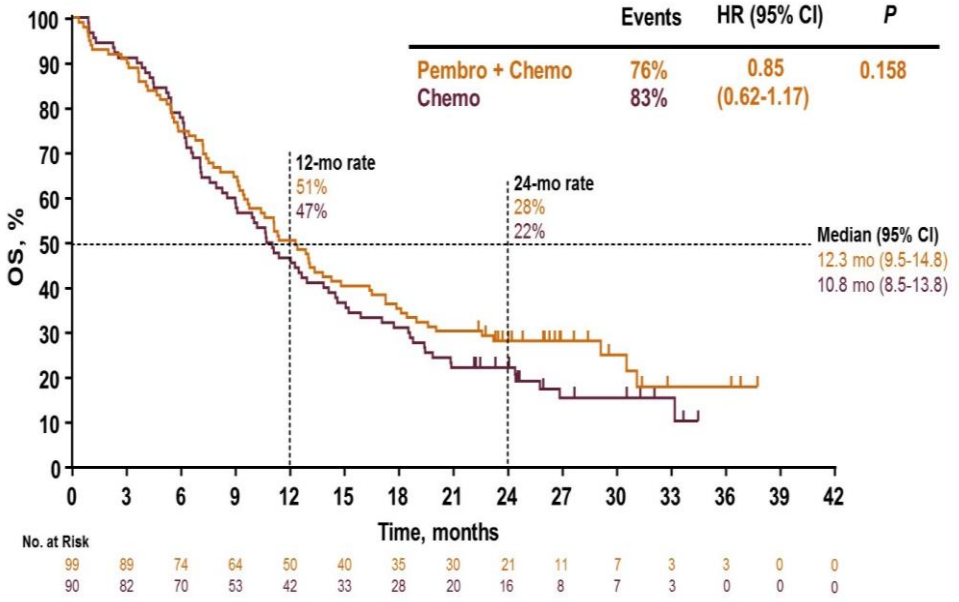
Overall Survival: P+C vs C (CPS ≥1)



Overall Survival: P+C vs C (CPS ≥10)



- Comparison of the combination of chemotherapy + pembrolizumab vs chemotherapy alone did not show any improvement in OS, in CPS ≥ 1 and CPS ≥ 10 groups
- PFS was not improved by the addition of pembrolizumab

Data cutoff date: March 26, 2019.

C, chemotherapy; Chemo, chemotherapy; CI, confidence interval; CPS, combined positive score; HR, hazard ratio; OS, overall survival; P, pembrolizumab; Pembro, pembrolizumab; PFS, progression-free survival.

Presented by Josep Tabernero at 2019 ASCO Annual Meeting (Abstract LBA4007).

KEYNOTE-062: PEMBROLIZUMAB FIRST IN MSI-HIGH GASTRIC CANCER?

	MSS CPS ≥1			MSI-H CPS ≥1			MSI-H CPS ≥10		
	Pembro	Chemo	HR	Pembro	Chemo	HR	Pembro	Chemo	HR
ORR				57.1%	36.8%				
DOR				21.2 mo	7.0 mo				
PFS				11.2 mo	6.6 mo	0.72			
OS	9.5 mo	11.2 mo	0.94	NR	8.5 mo	0.29	NR	13.6 mo	0.21

	MSI-H CPS ≥1			MSI-H CPS ≥10		
	Pembro + Chemo	Chemo	HR	Pembro + Chemo	Chemo	HR
ORR	64.7%	36.8%				
DOR	NR	7.0 mo				
PFS	NR	6.6 mo	0.45			
OS	NR	8.5 mo	0.37	NR	13.6 mo	0.26

CPS, combined positive score; Chemo, chemotherapy; DOR, duration of response; HR, hazard ratio; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NR, not reached; ORR, overall response rate; OS, overall survival; Pembro, pembrolizumab; PFS, progression-free survival.

Shitara K, et al. ESMO Congress 2019 abstract LBA44.

KEYNOTE-062: OVERALL SURVIVAL PEMBROLIZUMAB MONOTHERAPY

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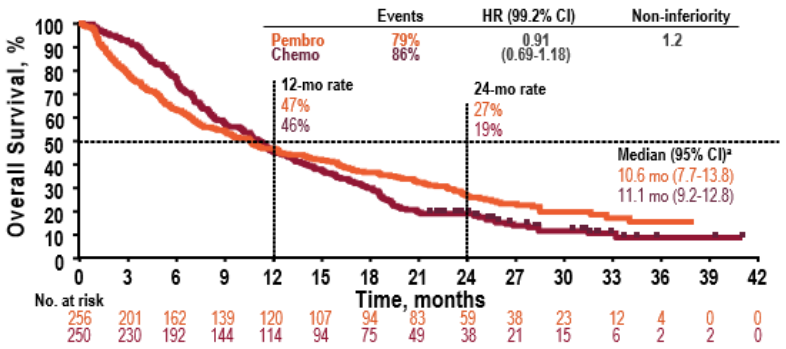
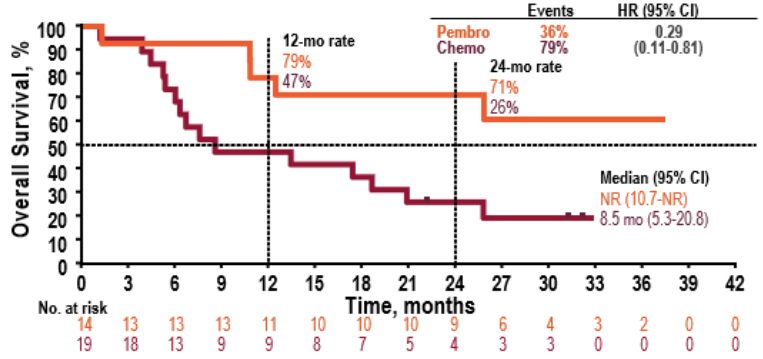
CPS ≥1

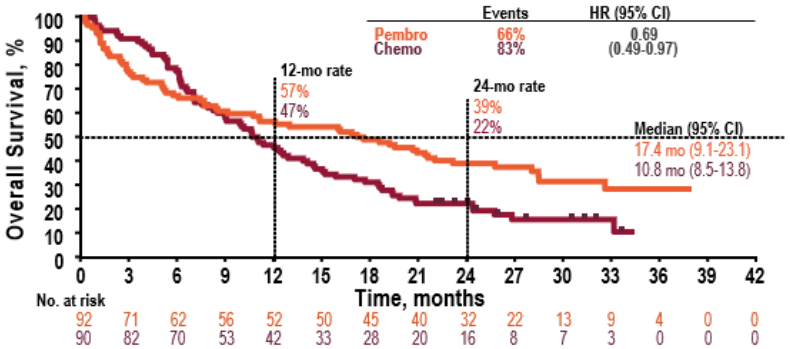
Overall

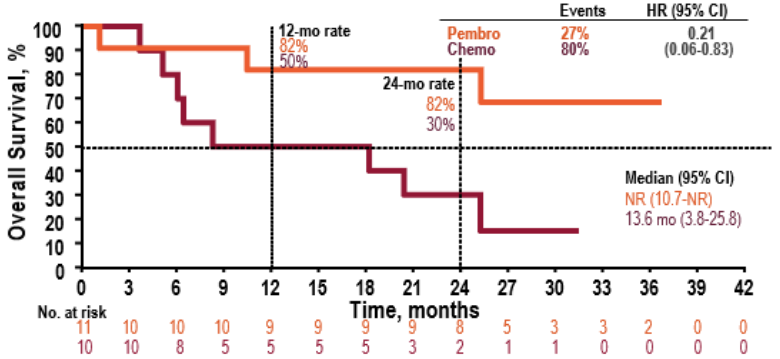


MSI-H Group



CPS ≥10





[a]HR (95% CI) = 0.91 (0.74-1.10); Data cutoff date: March 26, 2019.

CI, confidence interval; CPS, combined positive score; Chemo, chemotherapy; HR, hazard ratio; MSI-H, microsatellite instability-high; NR, not reached; Pembro, pembrolizumab.

Chung HC, et al. ESMO Asia Congress 2019 abstract 125O.

KEYNOTE-062: OVERALL SURVIVAL PEMBROLIZUMAB + CHEMOTHERAPY

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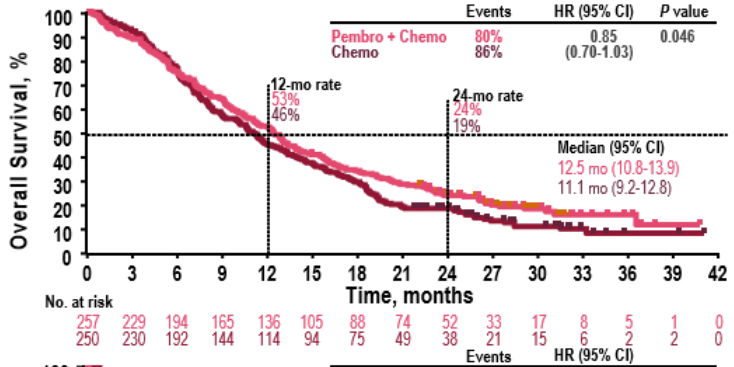
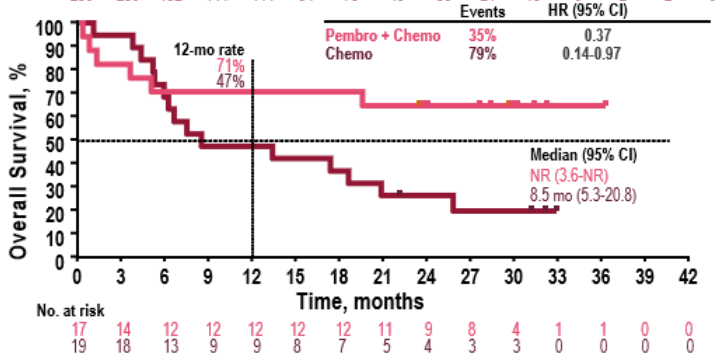
CPS ≥1

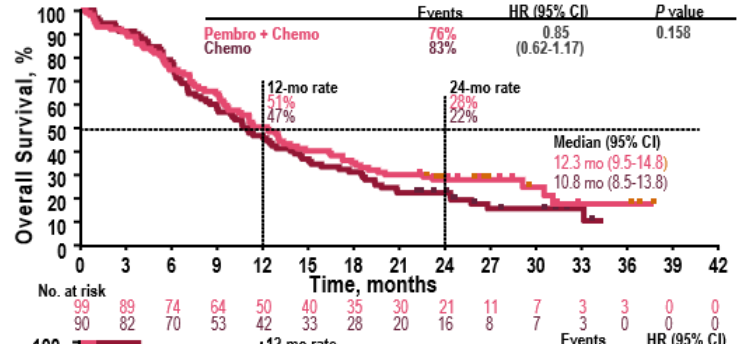
Overall

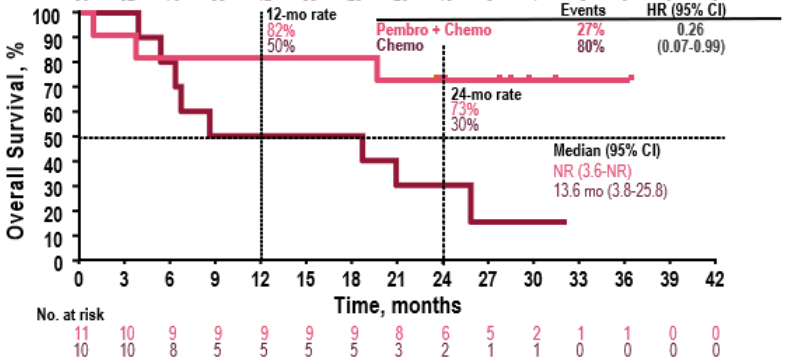


MSI-H Group



CPS ≥10





Data cutoff date: March 26, 2019.

CI, confidence interval; CPS, combined positive score; Chemo, chemotherapy; HR, hazard ratio; MSI-H, microsatellite instability-high; NR, not reached; Pembro, pembrolizumab.

Chung HC, et al. ESMO Asia Congress 2019 abstract 125O.

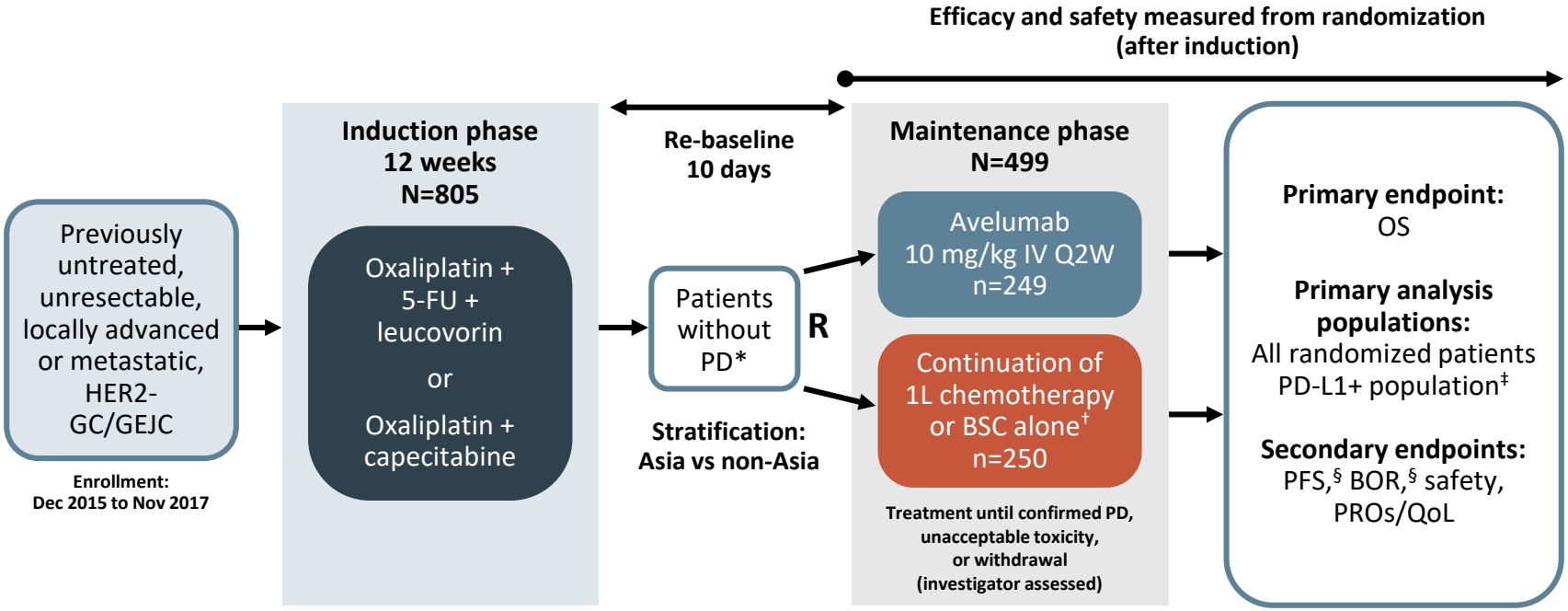
RESULTS OF THE JAVELIN GASTRIC 100 PHASE 3 TRIAL: AVELUMAB MAINTENANCE FOLLOWING FIRST-LINE (1L) CHEMOTHERAPY (CTx) VS CONTINUATION OF CTx FOR HER2– ADVANCED GASTRIC OR GASTROESOPHAGEAL JUNCTION CANCER (GC/GEJC)

Moehler, et al. ASCO GI 2020, abst #278

AVELUMAB – PD-L1 INHIBITOR THAT SHOWED ACTIVITY IN GASTRIC AND GEJ CANCERS

JAVELIN GASTRIC 100

AN INTERNATIONAL, OPEN-LABEL, PHASE 3 TRIAL



*Eligibility for randomization based on absence of PD was confirmed by an independent radiologist. †Choice of chemotherapy or BSC decided by investigators prior to randomization. ‡≥1% of tumor cells PD-L1+ using the 73-10 pharmDx assay (Dako). §Based on investigator assessment per RECIST 1.1.

1L, first-line; 5-FU, 5-fluorouracil; BOR, best overall response; BSC, best supportive care; GC/GEJC, gastric cancer/gastro-oesophageal junction cancer; HER2, human epidermal growth factor receptor 2; IV, intravenous; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand 1; PFS, progression-free survival; PRO, patient-reported outcome; Q2W, every 2 weeks; QoL, quality of life; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors.

Presented by Markus Moehler at 2020 ASCO GI Meeting (Abstract 278).

JAVELIN GASTRIC 100

- Patient's characteristics were well balanced between the 2 groups
- Very low numbers of patients with MSI-H tumors (14 in the avelumab arm vs. 8 in the chemotherapy arm)
- PD-L1 was positive (with 73-10 assay) in about 30% of patients

Results:

- Similar ORR in both arms: about 50% with CR or PR and almost 50% with SD
- Primary endpoint was not met with similar OS in both arms: median 10.4 vs. 10.9 months

CR, complete response; MSI-H, microsatellite instability-high; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease.

Presented by Markus Moehler at 2020 ASCO GI Meeting (Abstract 278).

JAVELIN GASTRIC 100

- Analysis by PD-L1 (73-10 assay) showed similar results and no survival advantage
- Analysis by CPS score ≥1 showed improved survival with avelumab (14.9 vs. 11.6 months), with end of the curve for avelumab and sustained benefit
- No difference in PFS
- AEs were as expected for each arm
- Duration of response was higher with avelumab
- Proportion of ongoing treatments was higher for avelumab:
  - 12-month rates for duration of response: 62.3% vs. 28.4%
  - 24-month rates for duration of response : 51% vs. 13%

AE, adverse event; CPS, combined positive score; PD-L1, programmed death ligand 1; PFS, progression-free survival.

Presented by Markus Moehler at 2020 ASCO GI Meeting (Abstract 278).

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