Colorectal & GE Cancers
Where are moving?

ESMO 2020

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ColoRectal Cancer

1. **Metastatic with MSI-High**
   - **PHASE III KEYNOTE 177 HRQOL**

Early CRC & Adjuvant therapy
   - **SUBGROUP ANALYSIS FROM TOSCA TRIAL**

GastroEsophageal Cancers

Metastatic Heur 2 (-)
   - **CHECKMATE 649**

Resectable & Adjuvant Rx
   - **CHECKMATE 577**

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- Colorectal Cancer is Heterogenous disease depending
  - Tumor Location, Molecular Profiling, Tumor Burden and The patient
- The Median survival for metastatic CRC is 30-36 months
  - (GI-ASCO 2020)
- The treatment Paradigm is an evolving process:
  - Bi-Chemotherapy , Tri-Chemotherapy with Anti-VEGF or Anti-EGFR
  - Targeted Agents and lastly PDL1-Inhibition thru Immunotherapy
- The behavior of Early CRC dictate the duration of systemic chemotherapy

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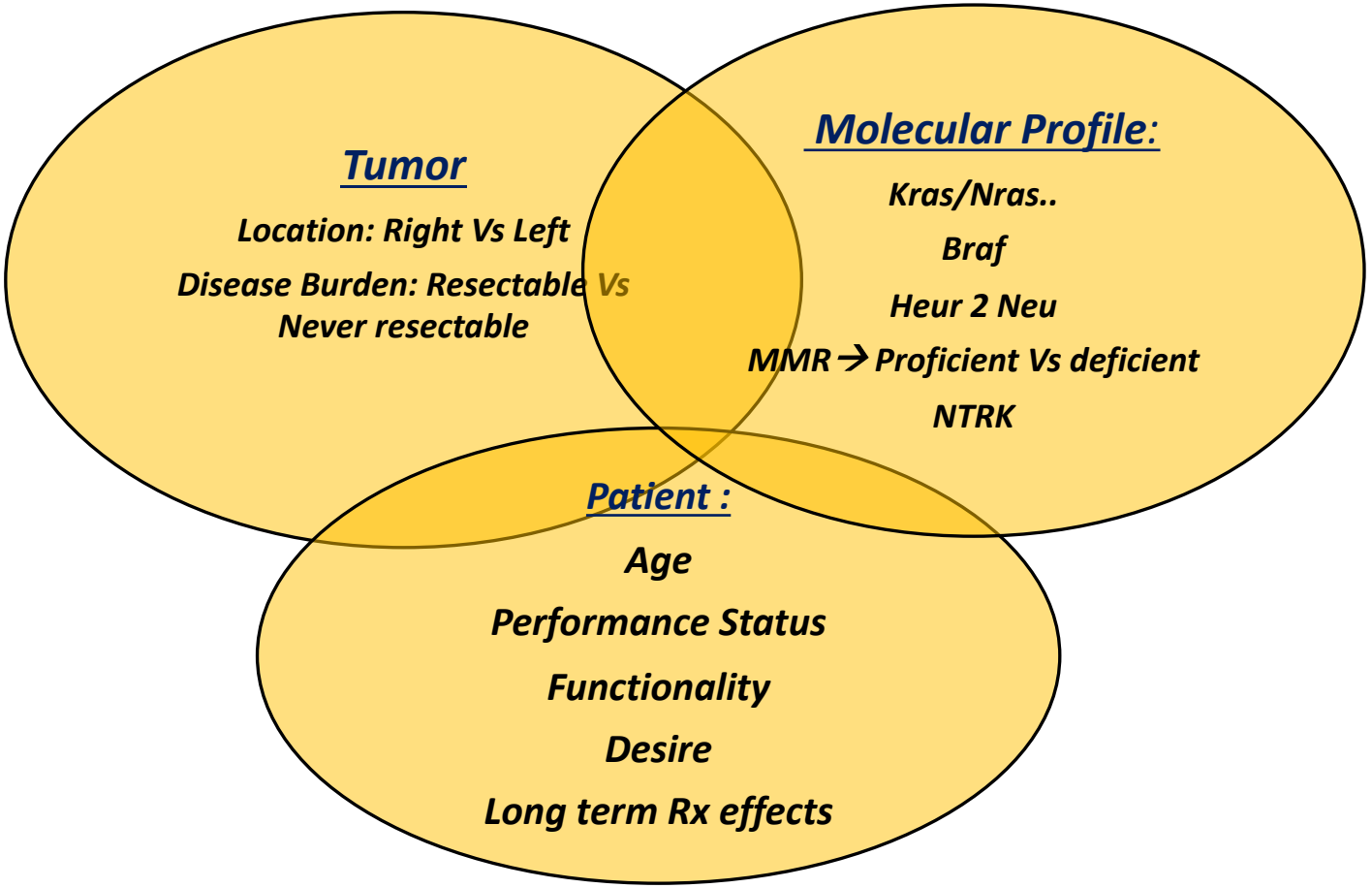

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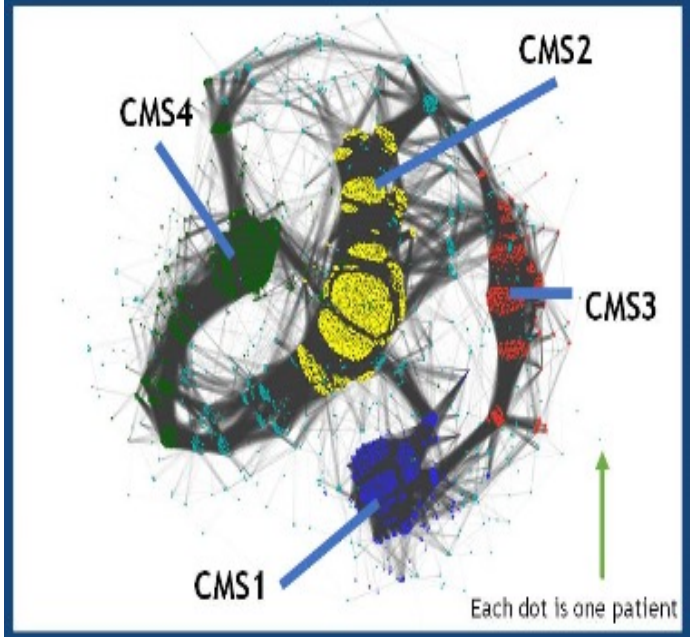


CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high Hypermutation	SCNA high	Mixed MSI status SCNA low, CIMP low	SCN high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration TGF beta activation Angiogenesis
Worse survival after relapse	Better survival after relaspe		Worse relapse-free and overall survival

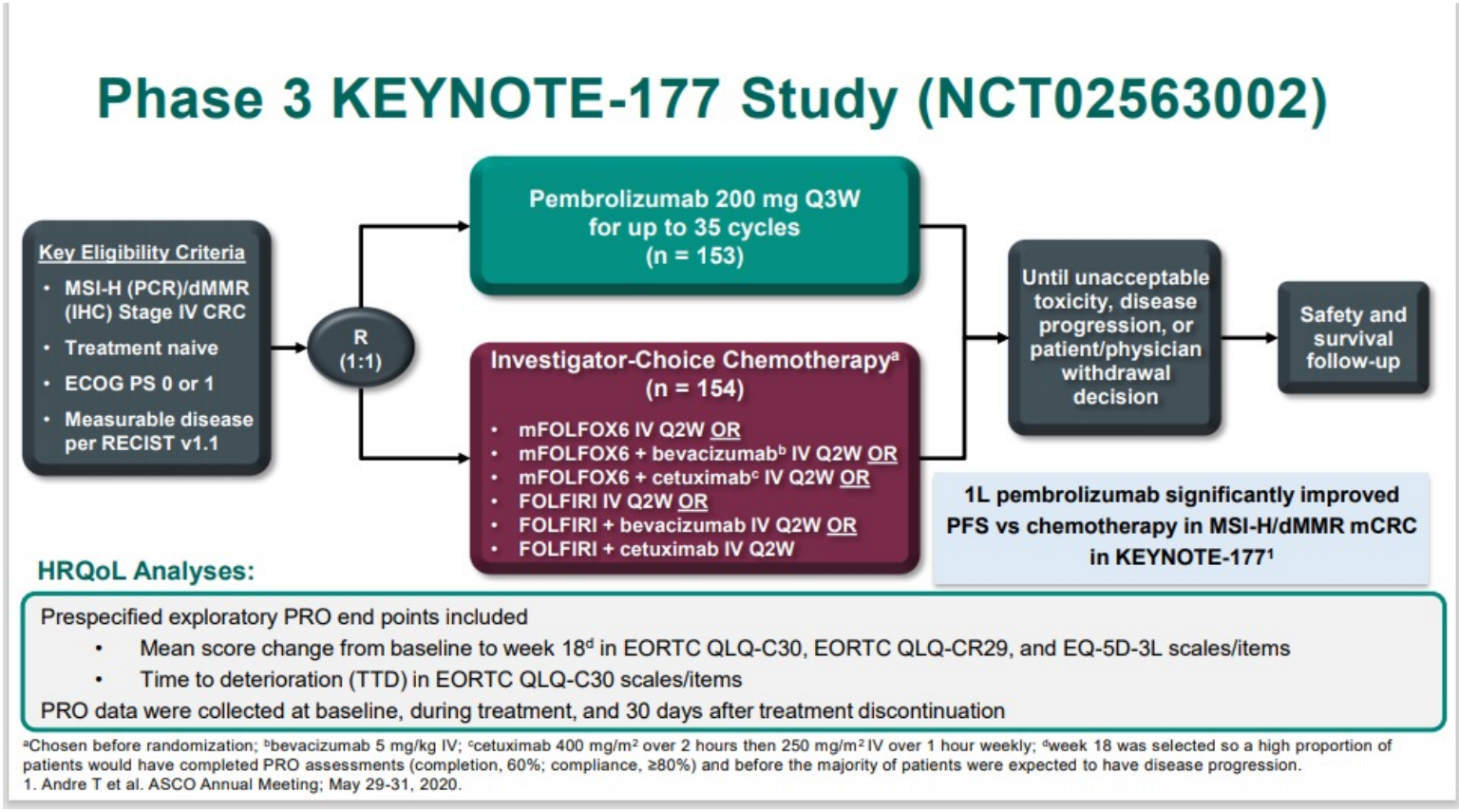
KEYNOTE 177 HRQOL

Pembrolizumab: Health-Related Quality of Life (KEYNOTE-177)

SUMMARY

- **KEYNOTE-177**[1] is a randomized, open label, phase 3 study of pembrolizumab monotherapy (N=152) versus standard of care (chemotherapy with or without bevacizumab or cetuximab, N=142) as first-line treatment in microsatellite-instability high (MSI-H)/mismatch repair deficient (dMMR) metastatic colorectal cancer.
- **Andre et al**[2] presented health-related quality of life results (HRQoL) from KEYNOTE-177. Patient-reported outcomes (PROs) were evaluated as prespecified exploratory endpoints (data cut-off date of February 19, 2020).
  - Least squares mean (LSM) change from baseline to week 18 showed improvement in the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) global health status/quality of life (GHS/QoL) scale with pembrolizumab versus chemotherapy (LSM difference: 8.96; p=0.0002).
  - Pembrolizumab prolonged time to deterioration (TTD) versus chemotherapy in GHS/QoL (Hazard ratio (HR), 0.61; p=0.0195), physical functioning (HR, 0.50; p=0.0016), social functioning (HR, 0.53; p=0.0050), and fatigue (HR, 0.48; p≤0.0001).

KEYNOTE 177 HRQOL



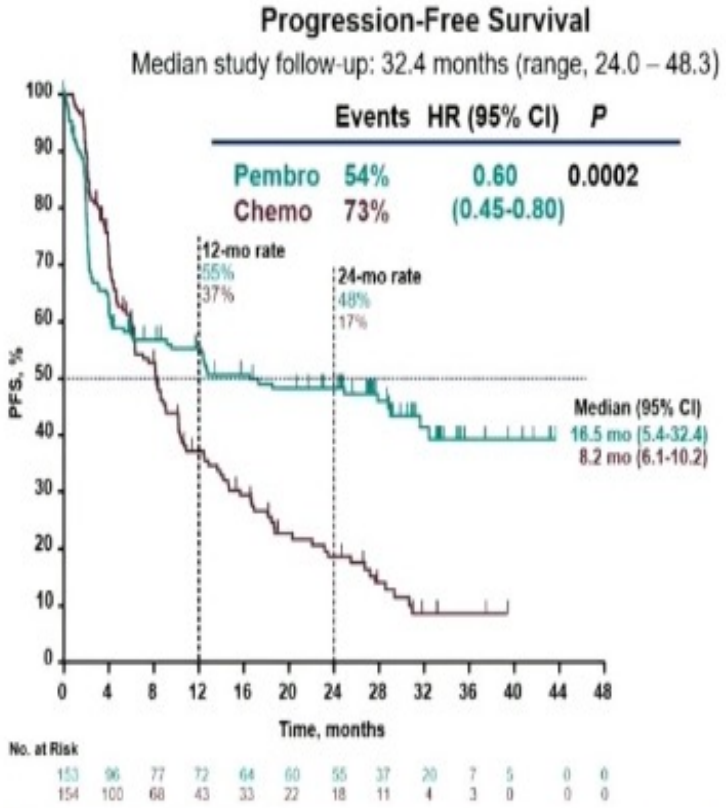
KEYNOTE 177 HRQOL

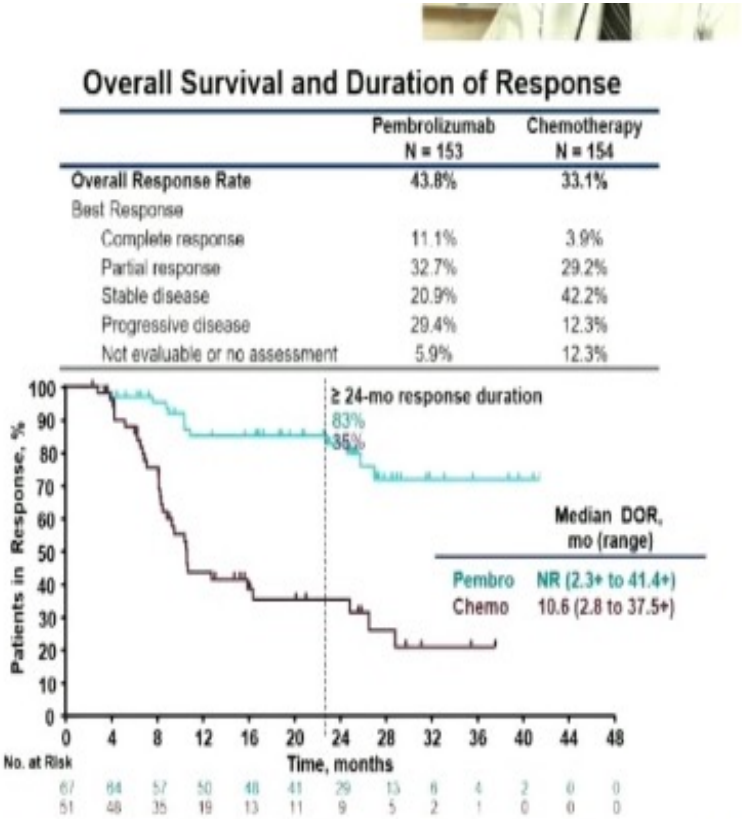
Mean Changes in PRO Scores

	EORTC QLQ-C30 GHS/QoL Score		EQ-5D VAS Score		EQ-5D Health Utility Score	
	Pembro	Chemo	Pembro	Chemo	Pembro	Chemo
Baseline						
Completed questionnaire, n	141	131	142	133	142	133
Mean score (SD)	66.19 (21.03)	66.60 (20.74)	70.12 (18.86)	70.83 (19.79)	0.77 (0.20)	0.75 (0.20)
Week 18						
Completed questionnaire, n	102	82	102	82	102	82
Mean score (SD)	72.14 (20.53)	62.60 (17.68)	76.86 (17.92)	70.76 (18.20)	0.84 (0.18)	0.77 (0.20)
Change from baseline[a]						
Included in analysis[b], n	151	141	151	141	151	141
LSM change from baseline (95%CI)	3.33 (–0.05 to 6.72)	–5.63 (–9.32 to –1.94)	4.50 (1.16 to 7.83)	–2.88 (–6.46 to 0.69)	0.04 (0.00 to 0.08)	–0.01 (–0.05 to 0.02)
LSM difference (95% CI) p-value[c]	8.96 (4.24 to 13.69) p=0.0002		7.38 (2.82 to 11.93) p=0.0016		0.05 (0.00 to 0.10) p=0.031	

CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core 30 items; EQ-5D, EuroQoL 5 Dimensions; LSM, least-squares mean; SD, standard deviation; VAS, visual analogue scale. [a]Based on a constrained longitudinal data analysis model with PRO scores as the response variable, and treatment by study visit interaction as covariates. [b]Analysis using constrained longitudinal data analysis model involved patients with at least one baseline or post-baseline assessment.[c]p values are 2-sided and nominal.

KEYNOTE 177 HRQOL

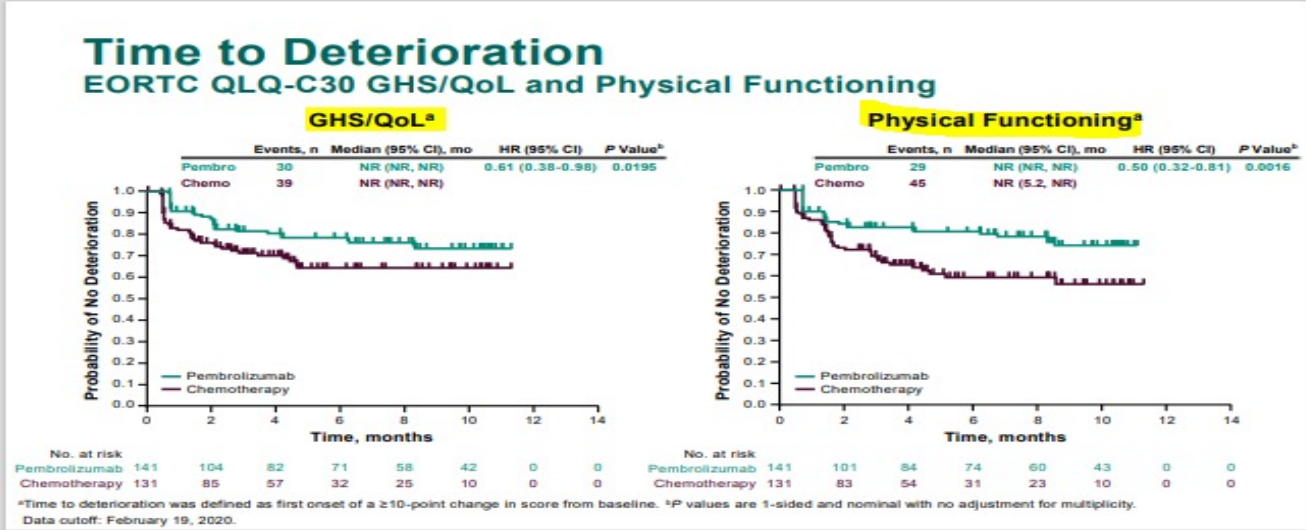


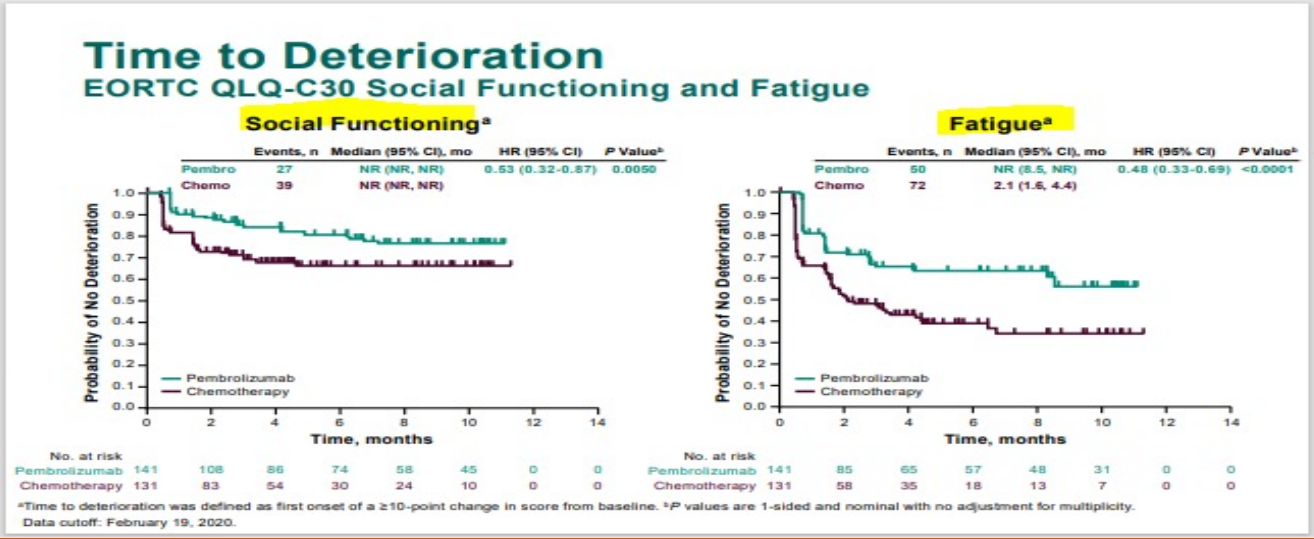


FS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR; uperiority of pembrolizumab vs chemotherapy in PFS was demonstrated at the pre-specified one-sided α = 0.0117; uration of response (DOR) assessed per RECIST v1.1 by BICR; Data cut-off: 19Feb2020.

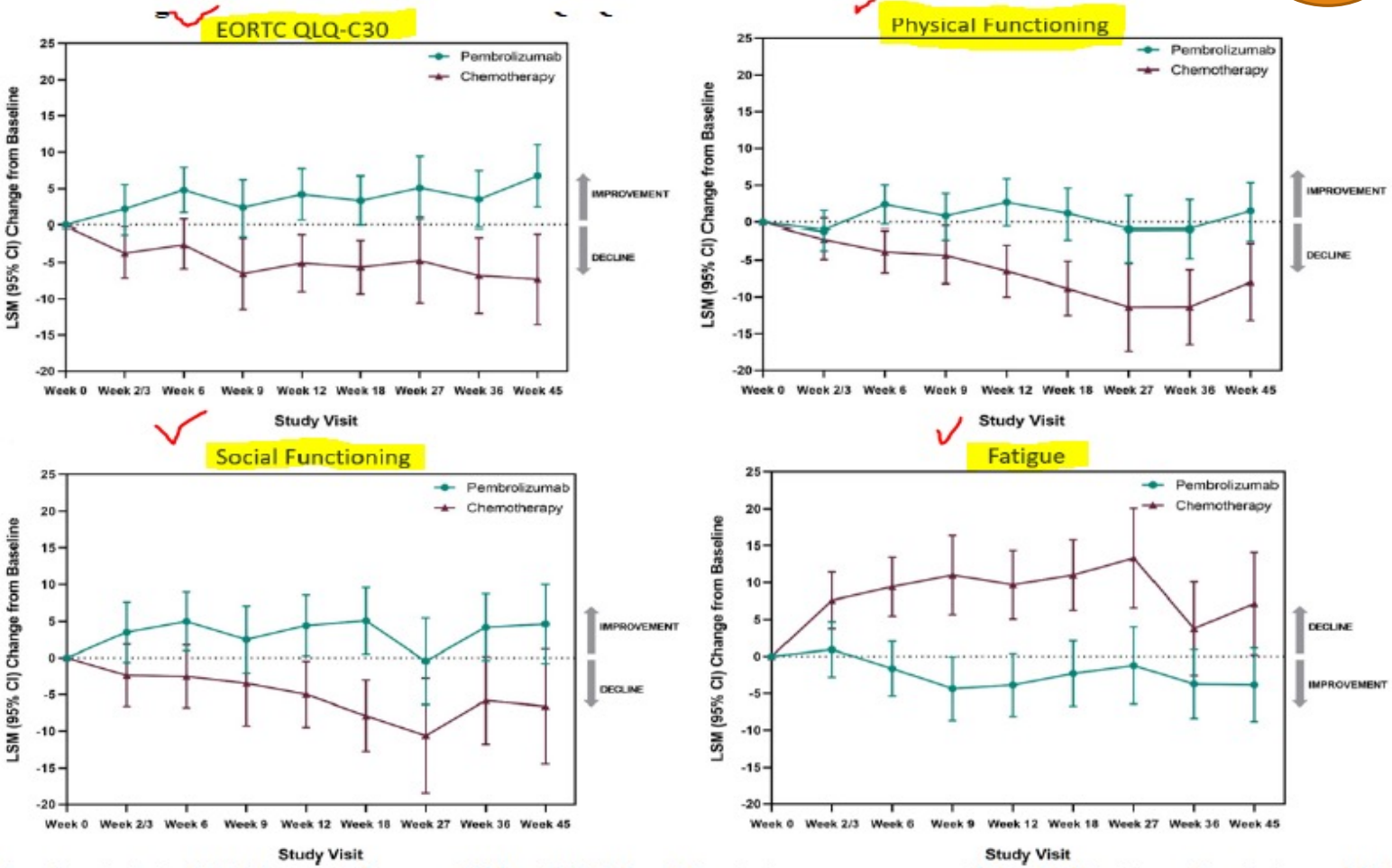
André T et al; ASCO 2020. *Clin Oncol.* 2020;38(supp

KEYNOTE 177 HRQOL





KEYNOTE 177 HRQOL



Error bars indicate 95% CIs around the mean. Higher GHS/QoL and functioning scores represent better health status or functioning and higher scores for fatigue indicates an increased severity of the symptom.

KEYNOTE 177 HRQOL

Conclusions

- Pembrolizumab monotherapy provided clinically meaningful improvements in HRQoL compared with chemotherapy ± bevacizumab or cetuximab in patients with previously untreated MSI-H/dMMR mCRC
  - Limitations include open label trial and PROs as exploratory end points
  - Results are mostly limited to treatment period
- HRQoL results complement the superior PFS and lower treatment-related adverse event rate with pembrolizumab versus chemotherapy ± bevacizumab or cetuximab
- These findings further support use of pembrolizumab as a standard of care for first-line treatment of patients with MSI-H/dMMR mCRC

FONDAZIONE GISCAD

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

OXALIPLATIN PLUS FLUOROPYRIMIDINES AS ADJUVANT THERAPY FOR COLON CANCER IN ELDERLY PATIENTS: A SUBGROUP ANALYSIS FROM TOSCA TRIAL

G. ROSATI, FA. GALLI, S. LONARDI, K.F. DOTTI, M. RONZONI, M.G. ZAMPINO, M. BANZI, V. PUSCEDDU, F. PASINI, S. BOZZARELLI, N. PELLA, C. CODECÀ, V. MONTESARCHIO, A. MAMBRINI, A. DE STEFANO, L. CIUFFREDA, S.E. REBUZZI, FR. GALLI, D. BILANCIA, R. LABIANCA

ON BEHALF OF ALL TOSCA (THREE OR SIX COLON ADJUVANT) INVESTIGATORS

TOSCA TRIAL subgroup Analysis ESMO 2020

- ✓ TOSCA[1] is a phase III non-inferiority trial randomizing 3759 patients within the IDEA[2] collaboration investigating adjuvant treatment duration in colon cancer.
- ✓ The study failed to show noninferiority of 3 vs 6 months of treatment to the predefined margin of 20% relative increase.
- ✓ However, a qualitative, non statistically significant interaction between regimen and treatment duration was observed: for CAPOX, 3 months were as good as 6 months; for FOLFOX, 6 months added extra benefit.
- ✓ The results of TOSCA Trial were consistent with those of the pooled analysis IDEA on more than 12.800 patients enrolled in 6 studies.

[1] Sobrero A et al, J Clin Oncol 2018
[2] Grothey A et al, N Engl J Med 2018

TOSCA TRIAL subgroup Analysis ESMO 2020

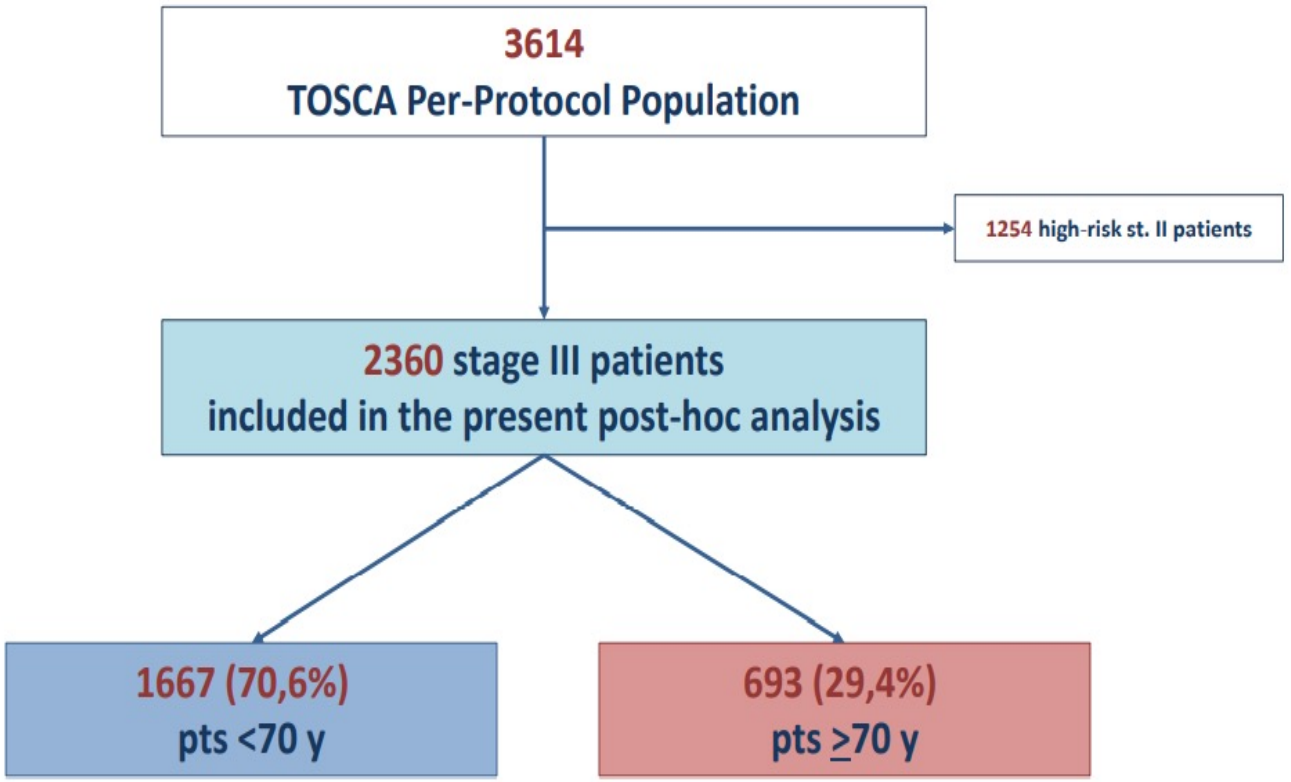
Objectives and endpoint

- ✓ To evaluate the impact of patients' age (< 70 vs ≥ 70 years old) on **efficacy** of OXA-based adjuvant chemotherapy in stage III colon cancer patients enrolled in TOSCA Trial, irrespective of randomization arm.
- ✓ To evaluate the **compliance** to the treatment

Primary End-Point: **Relapse-Free Interval**

defined as time from randomization to relapse or last disease evaluation

TOSCA TRIAL subgroup Analysis ESMO 2020

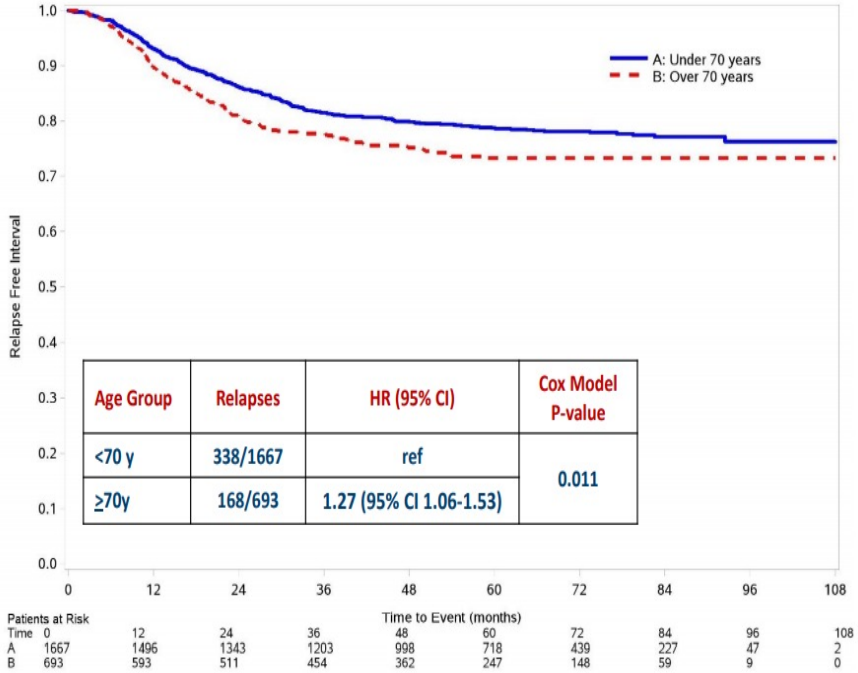


TOSCA TRIAL subgroup Analysis ESMO 2020

Events

	< 70 y. n = 1667	≥ 70 y. n = 693	Chi-square p-value
Follow-up (months)			-
Median	62.5	60.6	
Inter-quartile Range (1°-3°)	48.1-78.8	46.8-75.8	
Relapse – n (%)	338 (20.3)	168 (24.2)	0.033
Relapse site – n (%)			
Local	25 (7.5)	13 (7.7)	
Distant	293 (87.5)	142 (84.5)	
Both	17 (5.1)	13 (7.7)	
Missing	3	0	

Primary End-Point: Relapse-Free Interval



Age Group	Relapses	HR (95% CI)	Cox Model P-value
<70 y	338/1667	ref	0.011
≥70y	168/693	1.27 (95% CI 1.06-1.53)	

TOSCA TRIAL subgroup Analysis ESMO 2020

- The TOSCA Trial was a large trial including all age groups (> 70) randomized to 3 months Vs 6 months of adjuvant Chemotherapy
- A higher proportion of Relapse rate seen in Patients older than 70 as compared < 70 (24.2 % Vs 20.3 %) with P= 0.033
- The Multivariate analysis of the Relapse Free Interval did not indicate statistically significant effect of Age
- The small difference in relapse rate could be possibly attributed to compliance

CONCLUSION ESMO 2020 CRC

Take Home Message :

- **1. first-line therapy for MSI-H Metastatic colorectal cancer immunotherapy should be in new standard of care**
- **2. Keynote 177:**
  - **Median PFS 16.5 Vs 8.2 months (P= 0.002) Pembrozlimab Vs Chemotherapy with Bevacizumab/ Anti-EGFR Rx**
  - **Response rate 43.8% Vs 33.1 % (P= 0.0275) In favor Pembro**
  - **Lower Incidence of Grade 3 Rx related adverse events 22% Vs 66%**
- **3. TOSCA trial subgroup analysis patients > 70:**
  - **Multivariate analysis of the Relapse Free Interval did not indicate statistically significant effect of Age**
  - **Adjuvant Therapy Should be recommended to ALL Pts (including > 70) 3 months Vs 6 months based stratification T4 Vs T and N2 Vs N and chemoregimen FOLFOX Vs XELOX**

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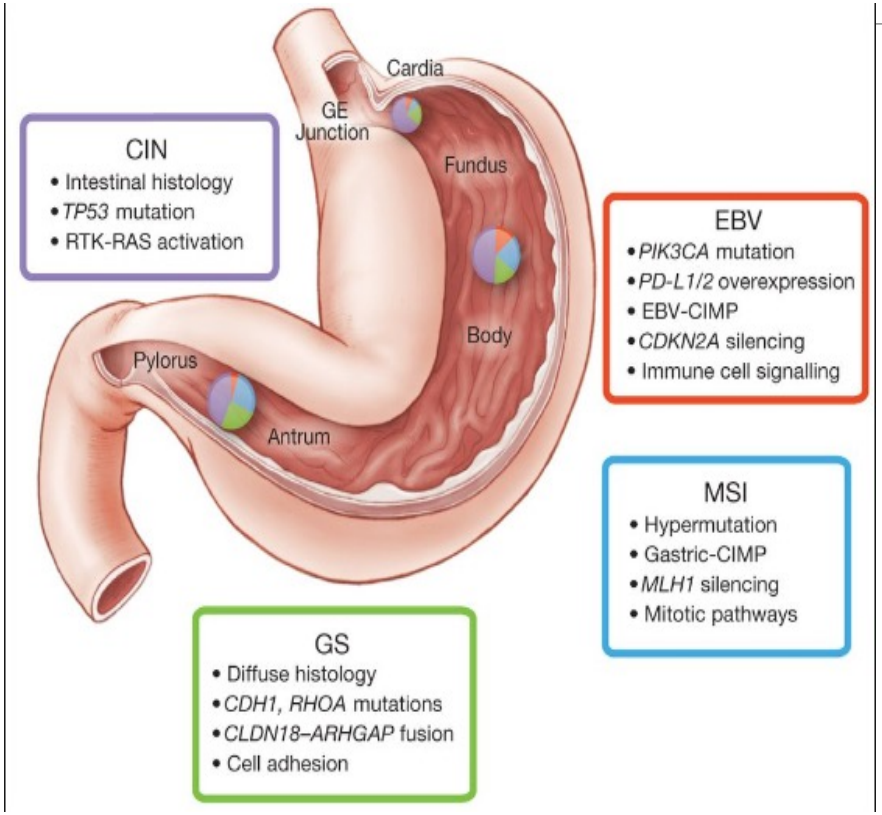
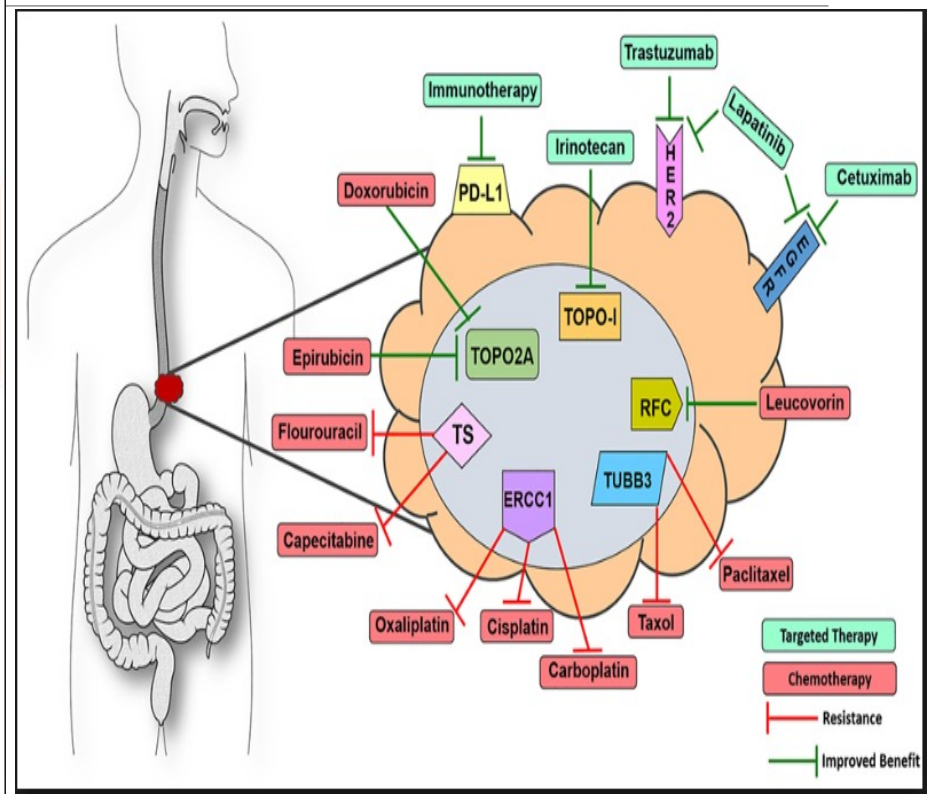
ESMO VIRTUAL CONGRESS 2020

- **Resectable & Adjuvant Rx**
  - **CHECKMATE 577 : Neoadjuvant chemo-XRT, surgery then adjuvant Nivo**
- **Metastatic Heur 2 (-)**
  - **CHECKMATE 649 : Nivo + chemo Vs Chemo in 1st L met . GE adenoca**
  - **ATTRACTION 4 Trial : in ASIA**
  - **KEYNOTE 590 : Pembro + chemo Vs Chemo**

Gastroesophageal Cancers





VIRTUAL 2020 ESMO congress

Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiation therapy: first results of the CheckMate 577 study

Ronan J. Kelly,[1] Jaffer A. Ajani,[2] Jaroslaw Kuzdzal,[3] Thomas Zander,[4] Eric Van Cutsem,[5] Guillaume Piessen,[6] Guillermo Mendez,[7] Josephine Feliciano,[8] Satoru Motoyama,[9] Astrid Lièvre,[10] Hope Uronis,[11] Elena Elimova,[12] Cecile Grootscholten,[13] Karen Geboes,[14] Jenny Zhang,[15] Lili Zhu,[15] Ming Lei,[15] Kaoru Kondo,[15] James M. Cleary,[16] Markus Moehler[17]

[1]The Charles A. Sammons Cancer Center at Baylor University Medical Center, Dallas, TX, USA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Jagiellonian University, John Paul II Hospital, Cracow, Poland; [4]University Hospital of Cologne, Cologne, Germany; [5]University Hospitals Gasthuisberg, Leuven and KULeuven, Leuven, Belgium; [6]University of Lille, Claude Huriez University Hospital, Lille, France; [7]Fundacion Favaloro, Buenos Aires, Argentina; [8]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [9]Akita University Hospital, Akita, Japan; [10]CHU Pontchaillou, Rennes 1 University, Rennes, France; [11]Duke Cancer Institute, Durham, NC, USA; [12]Princess Margaret Cancer Centre, Toronto, ON, Canada; [13]Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; [14]UZ Gent, Gent, Belgium; [15]Bristol Myers Squibb, Princeton, NJ, USA; [16]Dana Farber Cancer Institute, Boston, MA, USA; [17]Johannes-Gutenberg University Clinic, Mainz, Germany

Presentation number LBA9

CheckMate 577 study design

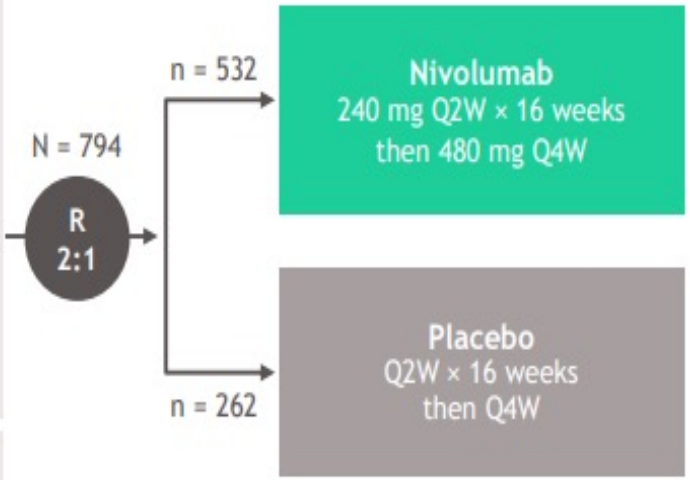
- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria

- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors

- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])



Total treatment duration of up to 1 year[d]

Primary endpoint:

- DFS[e]

Secondary endpoints:

- OS[f]
- OS rate at 1, 2, and 3 years

- Median follow-up was 24.4 months (range, 6.2-44.9)[g]
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

[a]ClinicalTrials.gov number, NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a pre-specified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]Time from randomization date to clinical data cutoff (May 12, 2020).

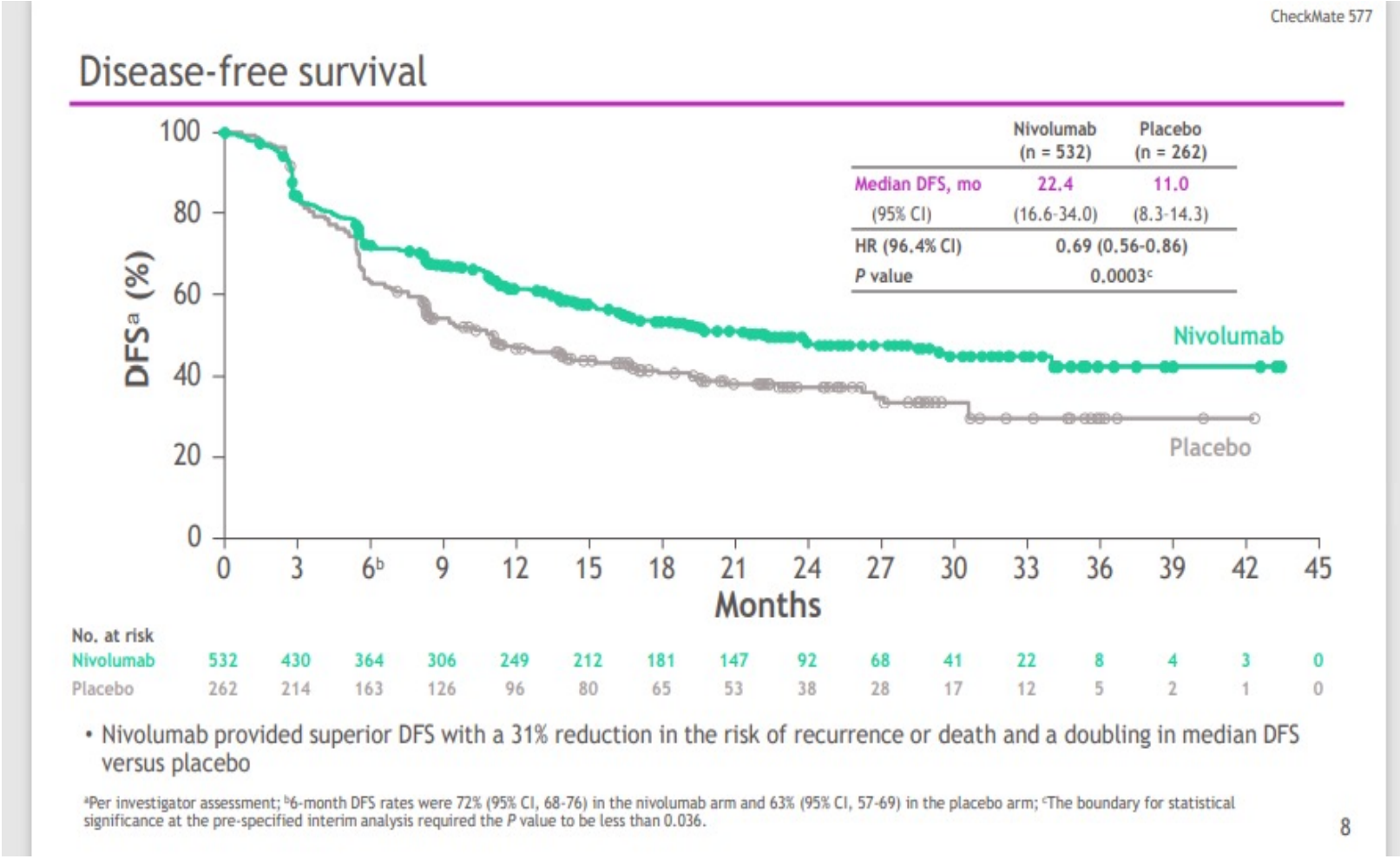
CHECKMATE 577 ESMO 2020

Baseline characteristics

	Nivolumab (n = 532)	Placebo (n = 262)
Median age (range), years	62.0 (26-82)	61.0 (26-86)
Male, %	84	85
Race,[a] %		
White	81	82
Asian	16	13
ECOG PS, %		
0	58	60
1	42	40
Disease stage at initial diagnosis, %		
II	34	38
III	66	62
Tumor location, %		
EC	60	59
GEJC	40	41
Histology, %		
Squamous cell carcinoma	29	29
Adenocarcinoma	71	71
Pathologic lymph node status ≥ ypN1, %	57	58
Tumor cell PD-L1 expression,[b] %		
≥ 1%	17	15
< 1%	70	75
Indeterminate/nonevaluable	13	10

[a]Other races not shown; [b]Tumor cell PD-L1 expression determined from surgical specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako).

CHECKMATE 577 ESMO 2020

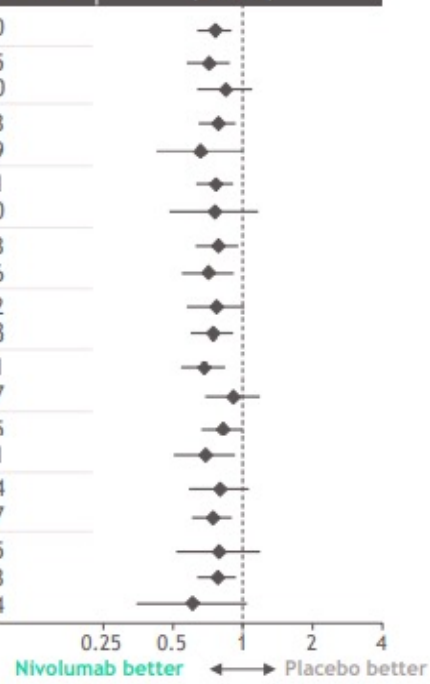


CHECKMATE 577 ESMO 2020

CheckMate 577

Disease-free survival by subgroups

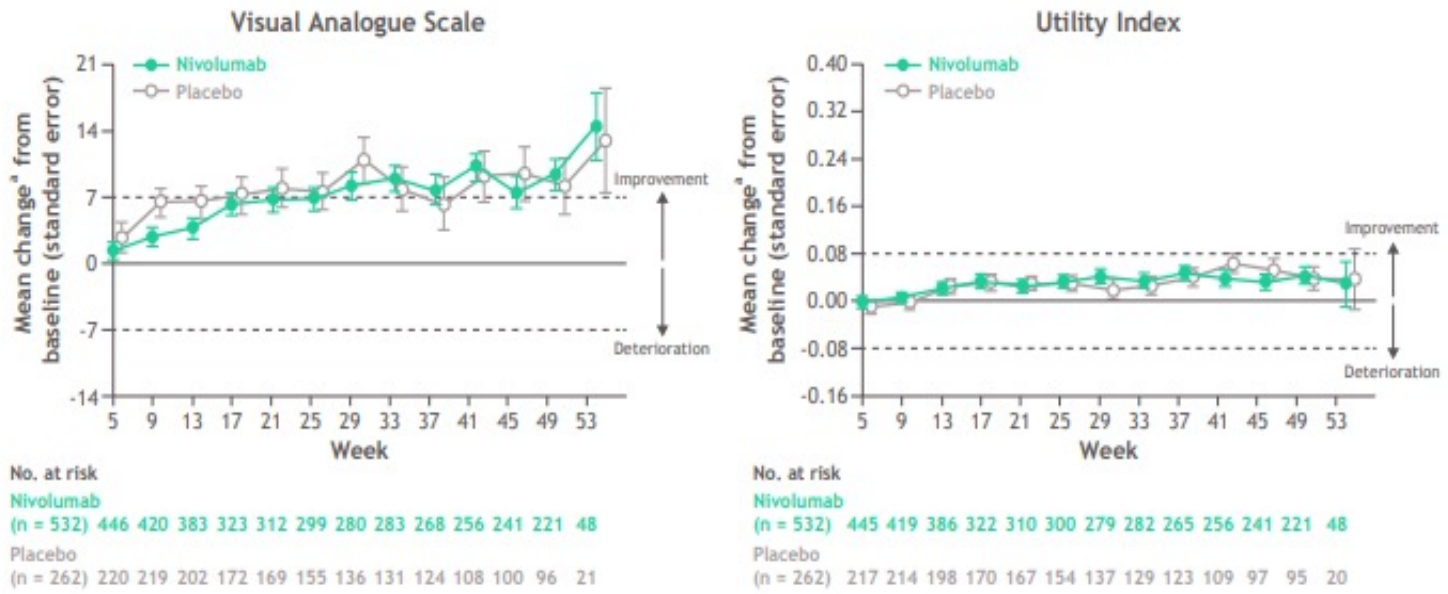
Subgroup		Median DFS, months		Unstratified HR
		Nivolumab	Placebo	
Overall (N = 794)		22.4	11.0	0.70
Age, years	< 65 (n = 507)	24.4	10.8	0.65
	≥ 65 (n = 287)	17.0	13.9	0.80
Sex	Male (n = 671)	21.4	11.1	0.73
	Female (n = 123)	Not reached	11.0	0.59
Race	White (n = 648)	21.3	10.9	0.71
	Asian (n = 117)	24.0	10.2	0.70
ECOG PS	0 (n = 464)	29.4	11.1	0.73
	1 (n = 330)	17.0	10.9	0.66
Disease stage at initial diagnosis	II (n = 278)	34.0	13.9	0.72
	III (n = 514)	19.4	8.5	0.68
Tumor location	EC (n = 462)	24.0	8.3	0.61
	GEJC (n = 332)	22.4	20.6	0.87
Histology	Adenocarcinoma (n = 563)	19.4	11.1	0.75
	Squamous cell carcinoma (n = 230)	29.7	11.0	0.61
Pathologic lymph node status	ypN0 (n = 336)	Not reached	27.0	0.74
	≥ ypN1 (n = 457)	14.8	7.6	0.67
Tumor cell PD-L1 expression	≥ 1% (n = 129)	19.7	14.1	0.75
	< 1% (n = 570)	21.3	11.1	0.73
	Indeterminate/nonevaluable (n = 95)	Not reached	9.5	0.54



- DFS favored nivolumab versus placebo across these pre-specified subgroups

CHECKMATE 577 ESMO 2020

Overall health status using the EQ-5D-3L



- Patient-reported outcome analyses revealed similar overall health status between nivolumab and placebo

[a]Descriptive analyses were conducted in all randomized patients who had an EQ-5D-3L visual analogue scale and utility index assessment at baseline and ≥ 1 postbaseline assessment. Changes from baseline of 7 and 0.08 points for the visual analogue scale and utility index, respectively, were considered clinically meaningful.[1]

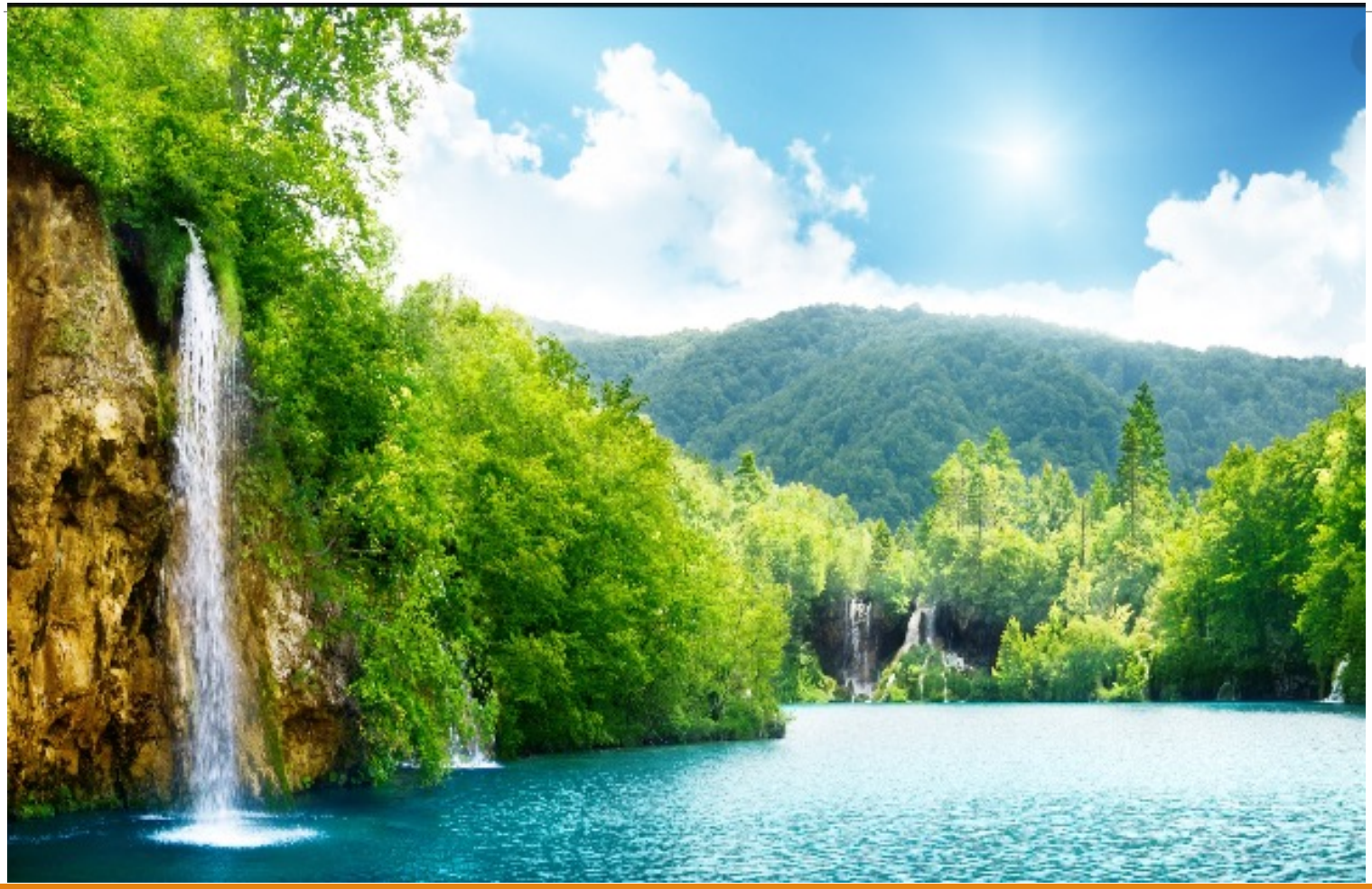
1. Pickard AS, et al. *Health Qual Life Outcomes* 2007;5:70.

CHECKMATE 577 ESMO 2020

Summary

- Nivolumab is the first adjuvant therapy to provide a statistically significant and clinically meaningful improvement in DFS versus placebo in resected EC/GEJC following neoadjuvant CRT
  - 31% reduction in the risk of recurrence or death and a doubling in median DFS
  - DFS benefit across multiple pre-specified subgroups
- Nivolumab was well tolerated with an acceptable safety profile
  - Incidence of serious TRAEs and TRAEs leading to discontinuation were ≤ 9% with nivolumab and 3% with placebo
- These results represent the first advance in years for this group of patients, potentially establishing adjuvant nivolumab as a new standard of care

Metastatic Esophageal Cancer ESMO 2020



VIRTUAL 2020 ESMO congress

Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: first results of the CheckMate 649 study

Markus Moehler,[1] Kohei Shitara,[2] Marcelo Garrido,[3] Pamela Salman,[4] Lin Shen,[5] Lucjan Wyrwicz,[6] Kensei Yamaguchi,[7] Tomasz Skoczylas,[8] Arinilda Campos Bragagnoli,[9] Tianshu Liu,[10] Michael Schenker,[11] Patricio Yanez,[12] Mustapha Tehfe,[13] Valerie Poulart,[14] Dana Cullen,[14] Ming Lei,[14] Kaoru Kondo,[14] Mingshun Li,[14] Jaffer A. Ajani,[15] Yelena Y. Janjigian[16]

[1]Johannes-Gutenberg University Clinic, Mainz, Germany; [2]National Cancer Center Hospital East, Kashiwa, Japan; [3]Clinica San Carlos de Apoquindo, Pontificia Universidad Católica, Chile; [4]Fundación Arturo López Pérez, Providencia, Chile; [5]Beijing Cancer Hospital, Beijing, China; [6]Klinika Onkologii i Radioterapii, Narodowy Instytut Onkologii, Warszawa, Poland; [7]Cancer Institute Hospital of JFCR, Tokyo, Japan; [8]II Klinika Chirurgii Ogólnej, Gastroenterologicznej i Nowotworów Układu Pokarmowego, Medical University of Lublin, Lublin, Poland; [9]Fundacao Pio Xii Hosp Cancer De Barretos, Barretos, Brazil; [10]Zhongshan Hospital Fudan University, Shanghai, China; [11]SF Nectarie Oncology Center, Craiova, Romania; [12]Universidad de La Frontera, Temuco, Chile; [13]Oncology Center - Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [14]Bristol Myers Squibb, Princeton, NJ, USA; [15]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [16]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA

Presentation number LBA6

CheckMate 649 study design

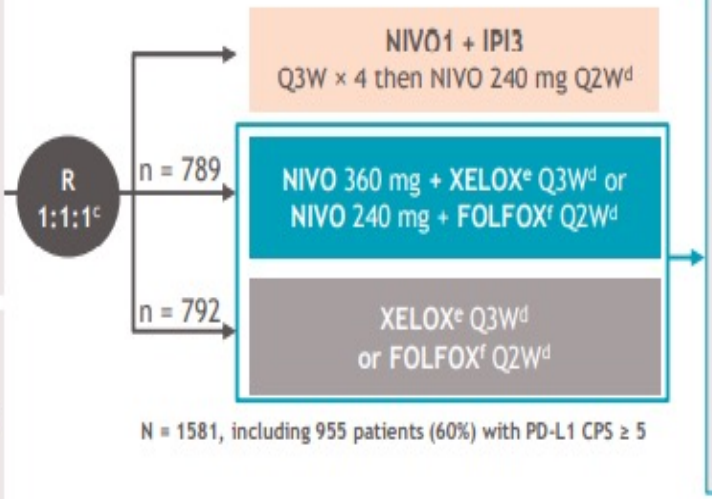
- CheckMate 649 is a randomized, open-label, phase 3 study[a]

Key eligibility criteria

- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0-1

Stratification factors

- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



Dual primary endpoints:

- OS and PFS[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:

- OS (PD-L1 CPS ≥ 1 or all randomized)
- OS (PD-L1 CPS ≥ 10)
- PFS[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- ORR[g]

- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

[a]ClinicalTrials.gov number, NCT02872116; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed; [d]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1-14); [f]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1-2); [g]BICR assessed; [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

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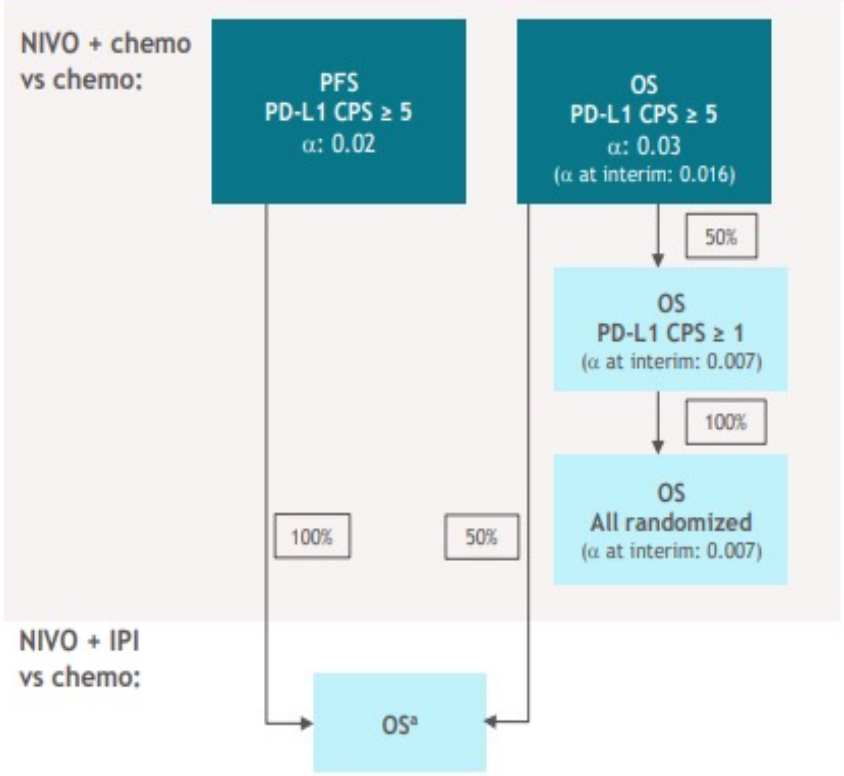
Statistical considerations



- Overall α is split between the 2 primary endpoints
- If OS in the PD-L1 CPS ≥ 5 population is statistically significant, OS in PD-L1 CPS ≥ 1, followed by OS in all randomized patients, is tested hierarchically
- Final PFS and pre-specified interim OS analyses: after a minimum follow-up of 12 months

Primary endpoint
Secondary endpoint
% Fraction of α transmitted to next endpoint

[a]Hierarchical testing of OS in the PD-L1 CPS ≥ 5 population, followed by all randomized patients, is planned for the final analysis.

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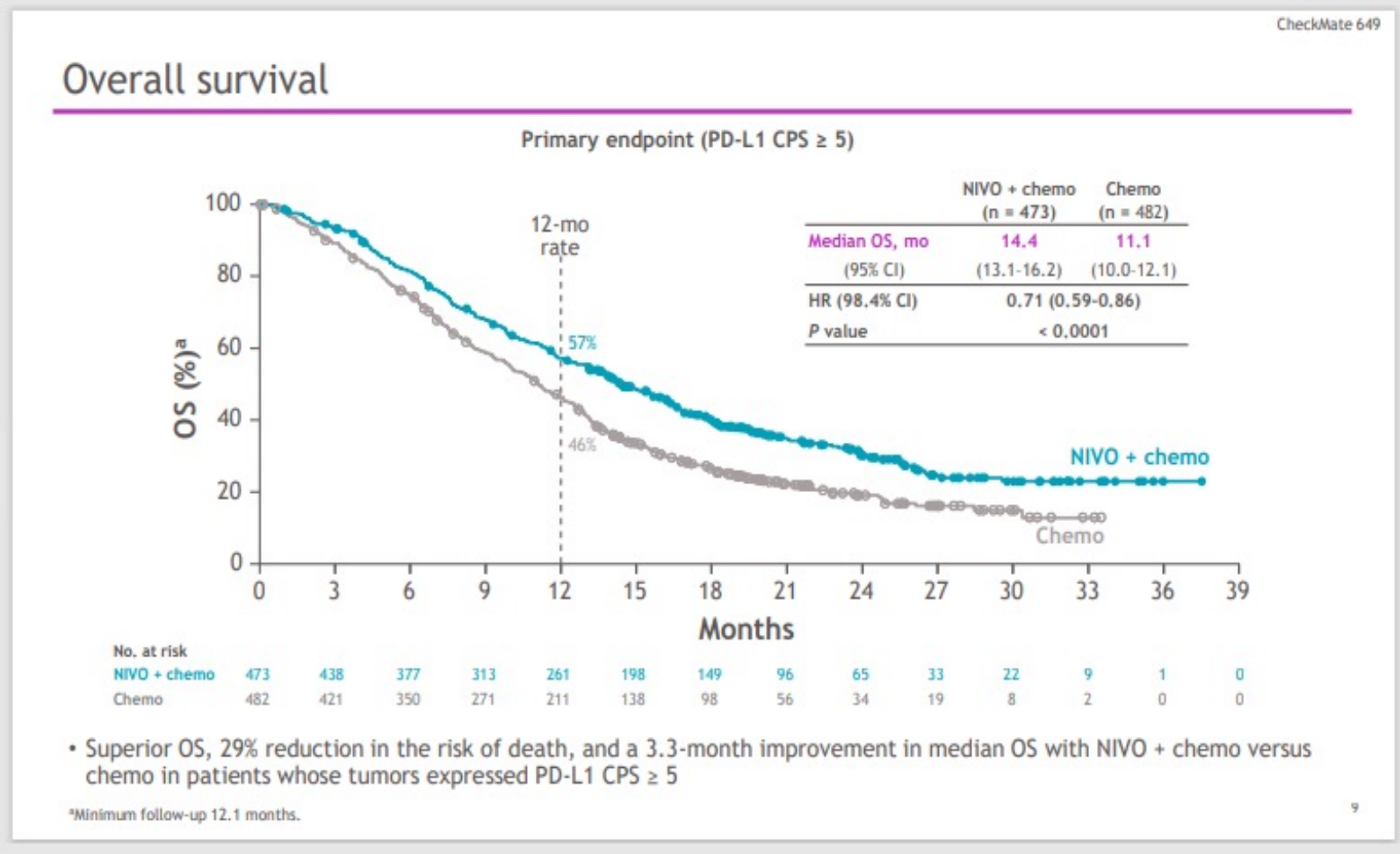

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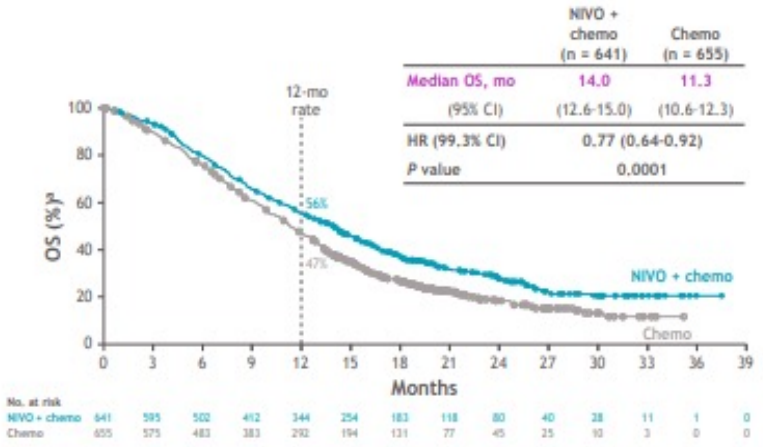
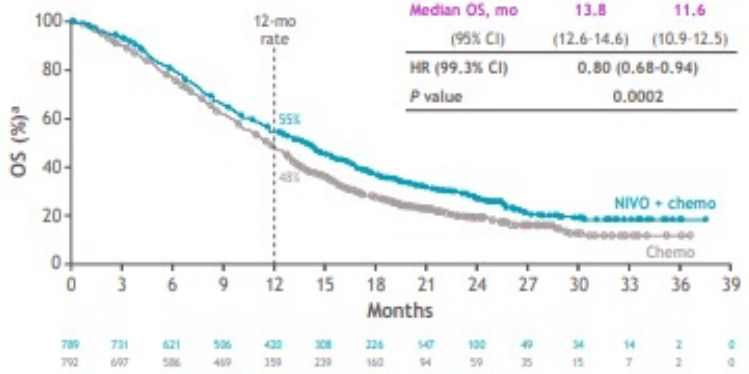
Overall survival

PD-L1 CPS ≥ 1



	NIVO + chemo (n = 641)	Chemo (n = 655)
Median OS, mo	14.0	11.3
(95% CI)	(12.6-15.0)	(10.6-12.3)
HR (99.3% CI)	0.77 (0.64-0.92)	
P value	0.0001	

All randomized



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS, mo	13.8	11.6
(95% CI)	(12.6-14.6)	(10.9-12.5)
HR (99.3% CI)	0.80 (0.68-0.94)	
P value	0.0002	

- Superior OS benefit in PD-L1 CPS ≥ 1 and all randomized patients with NIVO + chemo versus chemo

[a]Minimum follow-up 12.1 months.

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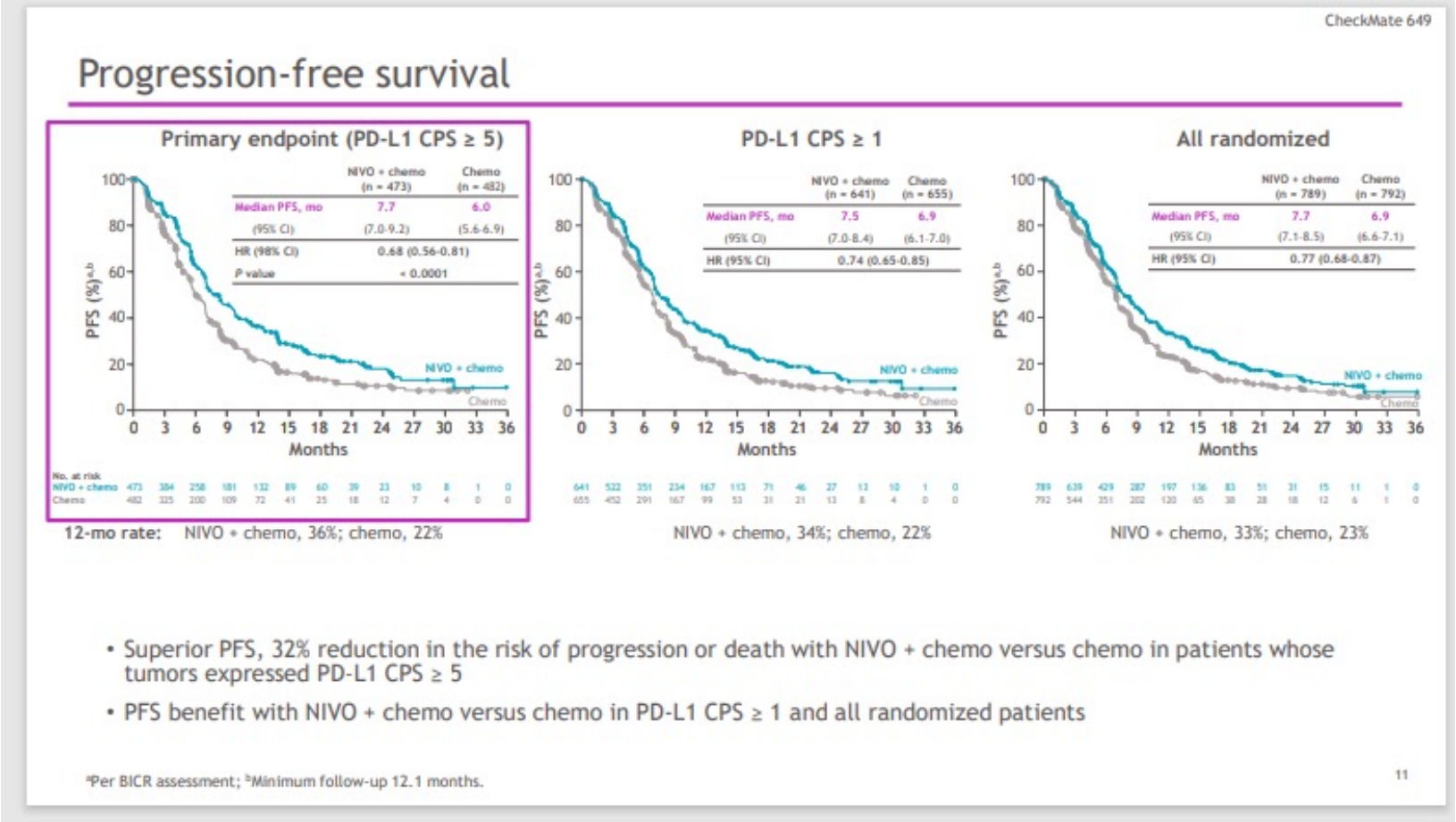

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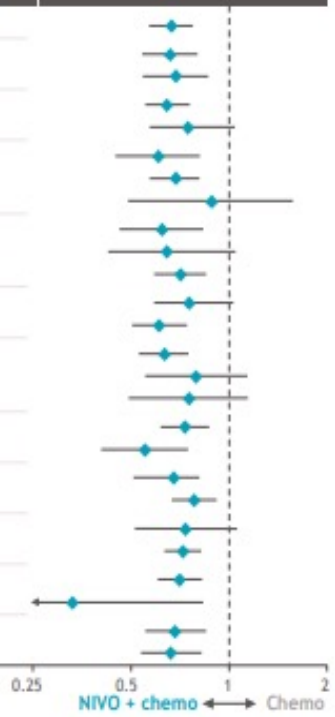
Overall survival subgroup analysis

Category (PD-L1 CPS ≥ 5)	Subgroup	Median OS, months		Unstratified HR for death
		NIVO + chemo	Chemo	
Overall (N = 955)		14.4	11.1	0.70
Age, years	< 65 (n = 552)	14.8	11.0	0.69
	≥ 65 (n = 403)	14.3	11.2	0.72
Sex	Male (n = 680)	14.4	10.8	0.67
	Female (n = 275)	14.4	12.1	0.78
Race	Asian (n = 236)	16.1	11.5	0.63
	White (n = 655)	14.0	11.1	0.71
	Other (n = 64)	9.8	10.6	0.93
Region	Asia (n = 228)	15.6	11.8	0.64
	US/Canada (n = 137)	16.8	12.6	0.67
	ROW (n = 590)	13.6	10.4	0.74
ECOG PS[a]	0 (n = 397)	17.6	13.8	0.79
	1 (n = 557)	12.6	8.8	0.63
Primary tumor location	GC (n = 667)	15.0	10.5	0.66
	GEJC (n = 170)	14.2	13.1	0.84
	EAC (n = 118)	11.2	11.3	0.78
Tumor cell PD-L1[b] expression	< 1% (n = 724)	14.2	11.6	0.75
	≥ 1% (n = 230)	16.2	8.8	0.56
Liver metastases	Yes (n = 408)	13.1	9.8	0.63
	No (n = 518)	15.5	12.0	0.76
Signet ring cell carcinoma	Yes (n = 141)	12.1	9.0	0.71
	No (n = 814)	15.1	11.3	0.69
MSI status[c]	MSS (n = 846)	14.4	11.1	0.73
	MSI-H (n = 34)	Not reached	8.8	0.33
Chemotherapy regimen	FOLFOX (n = 479)	14.3	11.3	0.71
	XELOX (n = 454)	15.0	11.0	0.69

Unstratified HR (95% CI)



- OS consistently favored NIVO + chemo versus chemo across multiple pre-specified subgroups

[a]Not reported, n = 1; [b]Unknown, n = 1; [c]Not reported/invalid, n = 75.

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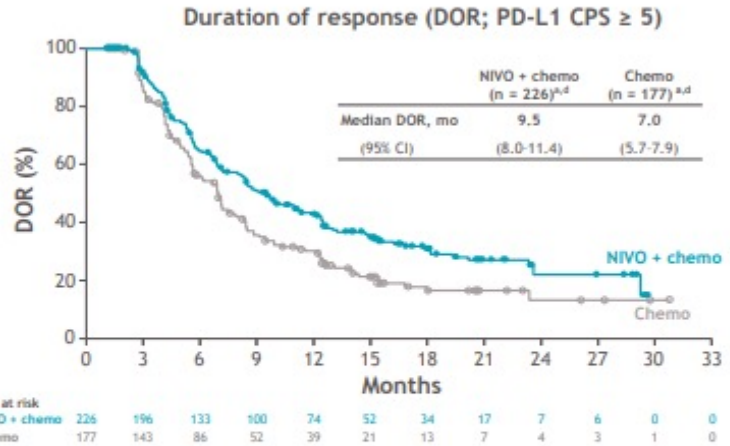
Response and duration of response

	PD-L1 CPS ≥ 5	
	NIVO + chemo (n = 378)[a]	Chemo (n = 391)[a]
ORR, %	60	45
95% CI	55-65	40-50
P value[b]	< 0.0001	
Best overall response,[c] %		
Complete response	12	7
Partial response	48	38
Stable disease	28	34
Progressive disease	7	11
Not evaluable	6	10
Median TTR (range), months	1.5 (0.8-10.2)	1.5 (1.0-7.1)



- ORR was higher with NIVO + chemo versus chemo, and responses were more durable

[a]Randomized patients who had target lesion measurements at baseline per BICR assessment; [b]ORR was not formally tested, the pre-specified *P* value is descriptive; [c]Percentages may not add up to 100% due to rounding; [d]Number of responders.

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Summary

- NIVO is the first PD-1–inhibitor to demonstrate superior OS and PFS in combination with chemo versus chemo alone in previously untreated patients with advanced GC/GEJC/EAC
  - Statistically significant and clinically meaningful OS benefit in patients whose tumors expressed PD-L1 CPS ≥ 5 and ≥ 1 and in all randomized patients
  - Survival benefit across multiple pre-specified subgroups (assessed in primary population)
  - PFS benefit in PD-L1 CPS ≥ 5 (statistically significant), PD-L1 CPS ≥ 1, and all randomized patients
- No new safety signals were identified with NIVO + chemo
- **NIVO + chemo represents a new potential standard 1L treatment for patients with advanced GC/GEJC/EAC**

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Nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced or recurrent gastric/ gastroesophageal junction (G/GEJ) cancer: ATTRACTION-4 (ONO-4538-37) study

N. Boku[1], M.H. Ryu[2], D.-Y. Oh[3], S.C. Oh[4], H.C. Chung[5], K.-W. Lee[6], T. Omori[7], K. Shitara[8], S. Sakuramoto[9], I.J. Chung[10], K. Yamaguchi[11], K. Kato[1], S.J. Sym[12], S. Kadowaki[13], K. Tsuji[14], J.-S. Chen[15], L.-Y. Bai[16], L.-T. Chen[17], Y.-K. Kang[2]

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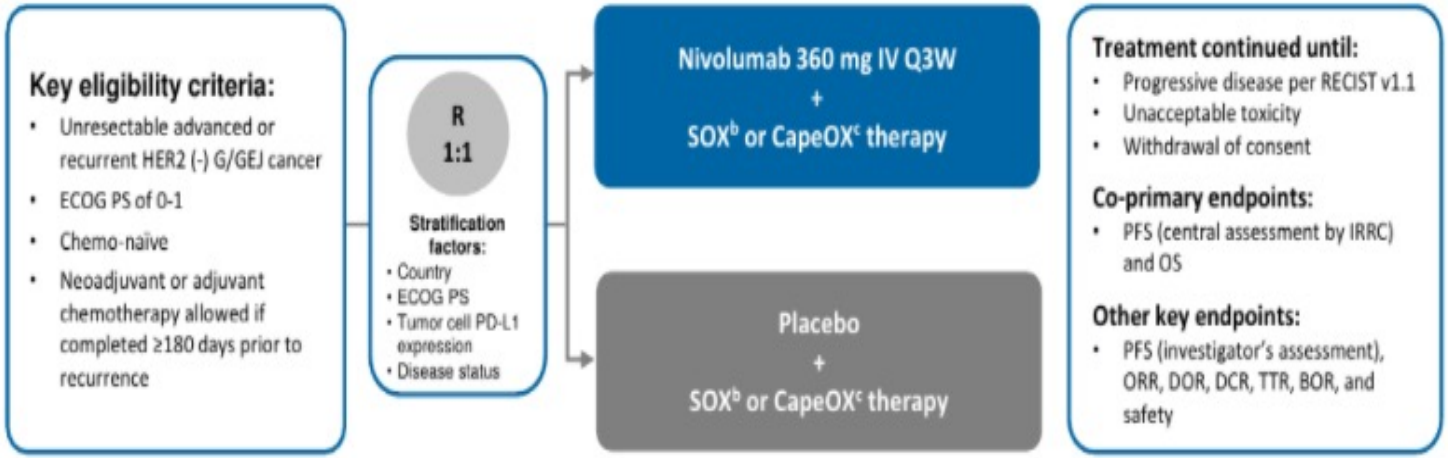
Phase 3 part of ATTRACTION-4: Study Design

- Phase 3 part of ATTRACTION-4 is a double-blind, randomized controlled study conducted at 130 centers in Japan, Korea, and Taiwan[a]



- At data cutoff for interim analysis of PFS (31 Oct 2018), the median follow-up period was 11.6 months
- At data cutoff for final analysis of OS (31 Jan 2020), the median follow-up period was 26.6 months
- A total of 724 patients were randomized between Mar 2017 and May 2018

[a]ClinicalTrials.gov Identifier: NCT02746796,
[b]SOX : S-1 (tegafur-gimeracil-oteracil potassium) 40 mg/m^2 orally twice daily (days 1–14) and Oxaliplatin 130 mg/m^2 IV (day 1), q3w
[c]CapeOX : Capecitabine 1000 mg/m^2 orally twice daily (days 1–14) and Oxaliplatin 130 mg/m^2 IV (day 1), q3w

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Exposure and Disposition

	Nivolumab + Chemotherapy (n = 359)		Placebo + Chemotherapy (n = 358)	
	Nivolumab + SOX (n = 229)	Nivolumab + CapeOX (n = 130)	Placebo + SOX (n = 230)	Placebo + CapeOX (n = 128)
Median Duration of treatment (range), months				
Nivolumab or Placebo	6.3 (0-32)	5.2 (0-33)	5.0 (0-31)	5.7 (0-33)
Oxaliplatin	5.4 (0-29)	4.9 (0-21)	4.6 (0-29)	4.9 (0-29)
S-1	7.1 (0-32)	-	5.4 (0-31)	-
Capecitabine	-	6.0 (0-33)	-	6.1 (0-34)
Discontinued Nivolumab or Placebo, n (%)	322 (89.7)		339 (94.7)	
Reason for Nivolumab or Placebo discontinuation, n (%)				
PD according to RECIST Guidelines (version 1.1)	212 (59.1)		252 (70.4)	
Worsening of clinical symptoms due to disease progression	19 (5.3)		22 (6.1)	
Unacceptable toxicity	30 (8.4)		17 (4.7)	
Investigator decision	31 (8.6)		15 (4.2)	
Other	41 (11.4)		44 (12.3)	
Subsequent pharmacotherapy, n (%)	230 (64.1)		244 (68.2)	
Nivolumab	37 (10.3)		91 (25.4)	
Pembrolizumab	5 (1.4)		7 (2.0)	

SOX, S-1 (Tegafur-gimeracil-oteracil potassium) plus oxaliplatin combination; CapeOX, Capecitabine plus oxaliplatin combination; PD, Progression of disease

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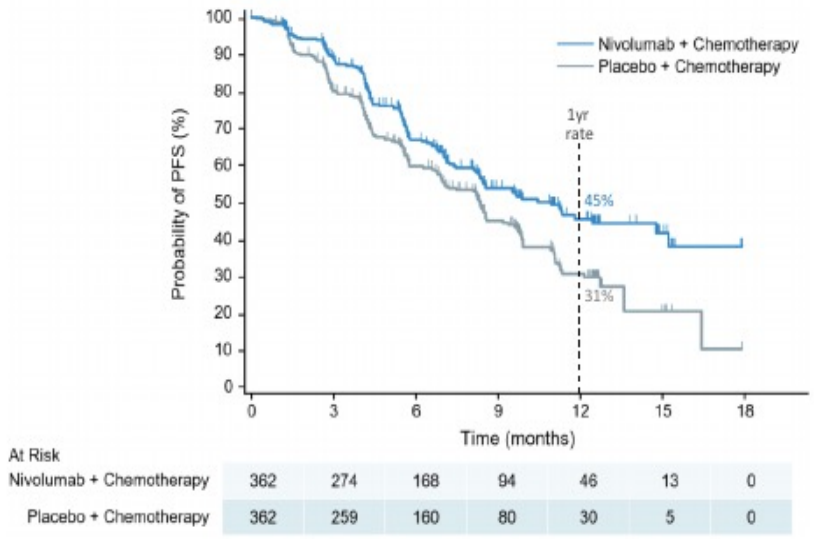
Progression-Free Survival (Interim Analysis)



	Nivolumab + Chemotherapy N = 362	Placebo + Chemotherapy N = 362
Median PFS, months (95% CI)	10.45 (8.44-14.75)	8.34 (6.97-9.40)
Hazard ratio (98.51% CI)	0.68 (0.51-0.90)	
P value	0.0007	
1yr PFS rate (%)	45.4	30.6

Data cut off : 31 Oct 2018 at interim analysis

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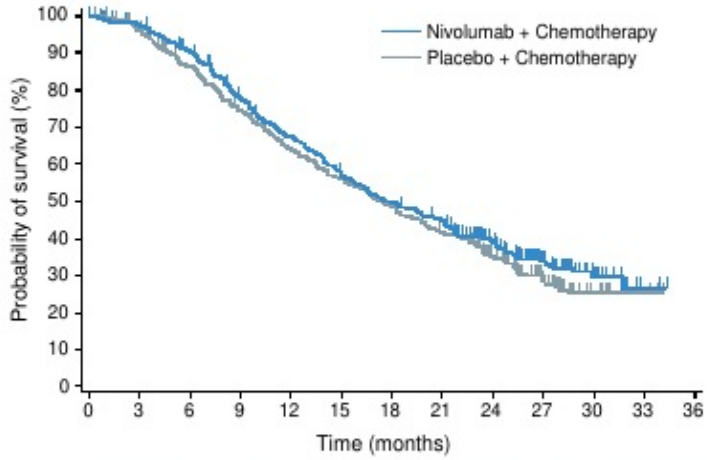
Overall Survival (Final Analysis)



At Risk													
Nivolumab + Chemotherapy	362	346	318	269	232	193	169	150	102	58	23	2	0
Placebo + Chemotherapy	362	342	301	259	219	192	167	141	97	48	16	5	0

	Nivolumab + Chemotherapy N = 362	Placebo + Chemotherapy N = 362
Median OS, months (95% CI)	17.45 (15.67-20.83)	17.15 (15.18-19.65)
Hazard ratio (95% CI)	0.90 (0.75-1.08)	
P value	0.257	

Data cut off : 31 Jan 2020 at final analysis

ATTRACTION 4 TRIAL ESMO 2020

ATTRACTION-4

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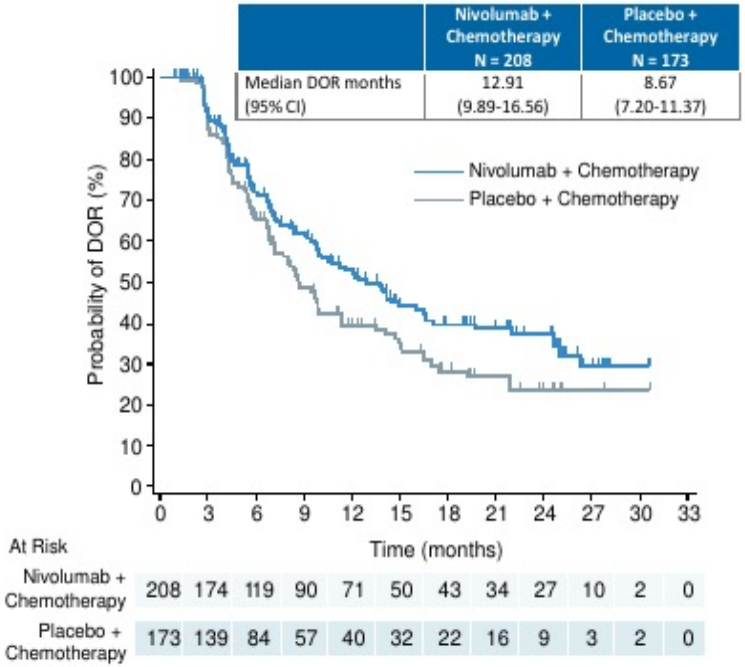
Overall response rate and duration of response

	Nivolumab + Chemotherapy N = 362	Placebo + Chemotherapy N = 362
ORR, n (%)	208 (57.5)	173 (47.8)
95% CI	52.2-62.6	42.5-53.1
P value	0.0088	
Best overall response, n (%)		
Complete response	70 (19.3)	48 (13.3)
Partial response	138 (38.1)	125 (34.5)
Stable disease	52 (14.4)	75 (20.7)
Progressive disease	25 (6.9)	46 (12.7)
Not evaluable*	77 (21.3)	68 (18.8)
DCR, n (%)	260 (71.8)	248 (68.5)
95% CI	66.9-76.4	63.4-73.3
Median TTR (range), months	1.4 (1.0-8.3)	1.4 (1.0-15.3)

CI, confidence interval; DCR, disease control rate; DOR, duration of response; ORR, overall response rate; TTR, time to response

*Patients without image examination for response evaluation, without change in tumors assessable for response, or without measurable lesions judged by the central review.



Data cut off : 31 Jan 2020 at final analysis

ATTRACTION 4 TRIAL ESMO 2020

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Summary and Conclusion

- NIVO + Chemo demonstrated a statistically significant improvement in PFS, but not in OS
  - Higher overall response rates and more durable responses
- The pre-specified objective of the phase 3 part of ATTRACTION-4 was achieved, showing clinically meaningful efficacy
- NIVO + Chemo demonstrated a manageable safety profile
- NIVO + Chemo could be considered a new first-line treatment option in unresectable advanced or recurrent G/GEJ cancer

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ESMO > Meetings > Past Meetings

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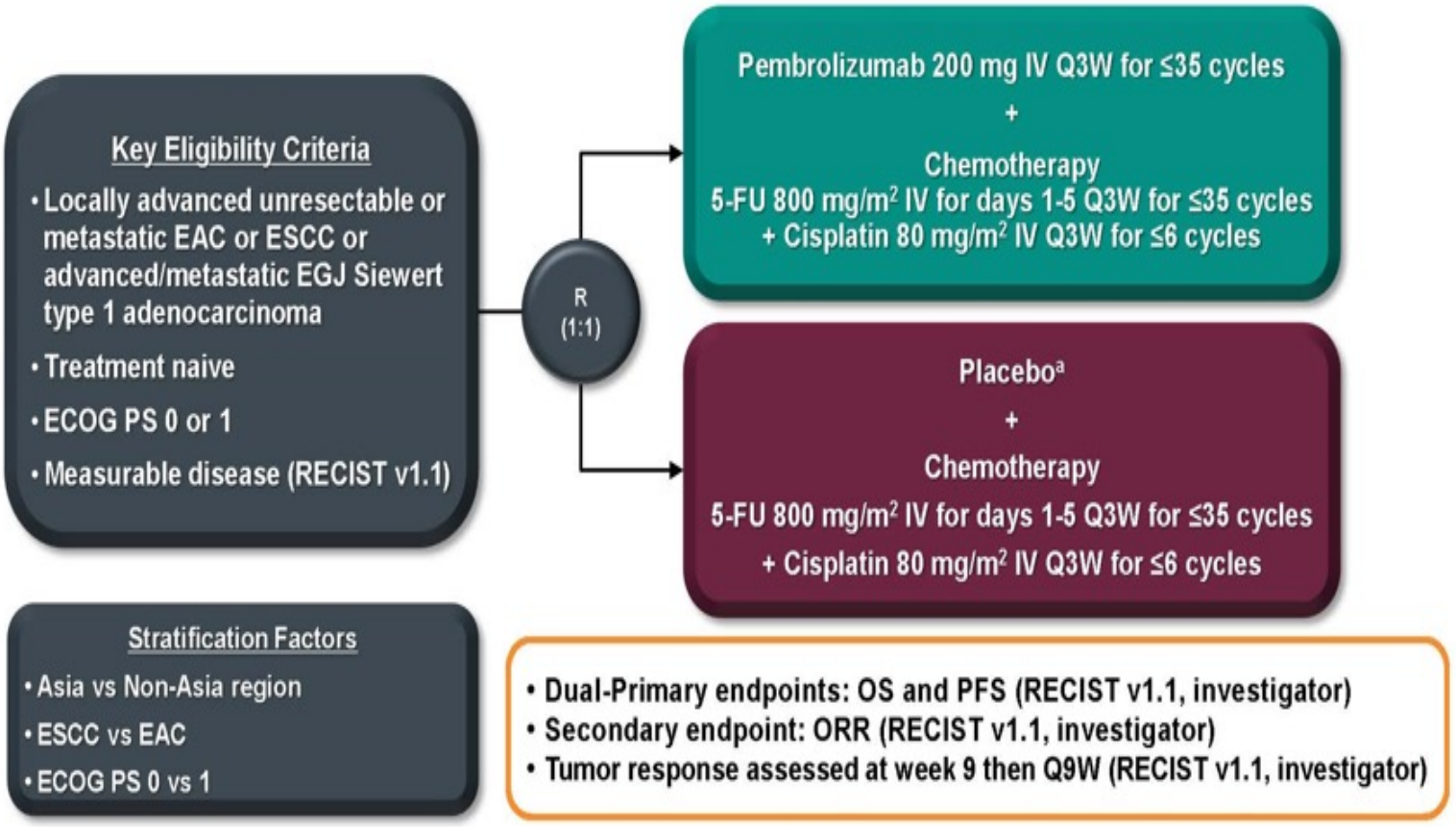
Pembrolizumab Plus Chemotherapy Versus Chemotherapy as First-Line Therapy in Patients With Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study

Ken Kato,[1] Jong-Mu Sun,[2] Manish A. Shah,[3] Peter Enzinger,[4] Antoine Adenis,[5] Toshihiko Doi,[6] Takashi Kojima,[6] Jean-Philippe Metges,[7] Zhigang Li,[8] Sung-Bae Kim,[9] Byoung Chul Cho,[10] Wasat Mansoor,[11] Shau-Hsuan Li,[12] Patrapim Sunpaweravong,[13] Maria Alsina Maqueda,[14] Eray Goekkurt,[15] Qi Liu,[16] Sukrut Shah,[16] Pooja Bhagia,[16] Lin Shen[17]

[1]National Cancer Center Hospital, Tokyo, Japan; [2]Samsung Medical Center, Sungkyunkwan University Seoul, Republic of Korea, [3]Weill Cornell Medical College, New York, NY, USA; [4]Dana Farber Cancer Institute, Boston, MA, USA; [5]IRCM, Inserm, Université Montpellier, ICM, Montpellier, France; [6]National Cancer Center Hospital East, Kashiwa, Japan;[7]CHU Brest – Institut de Cancerologie et d'Hematologie ARPEGO Network, Brest, France; [8]Shanghai Chest Hospital Esophageal Disease Center, Shanghai, China; [9]Asan Medical Center, Seoul, Republic of Korea; [10]Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea; [11]Christie Hospital NHS Trust, Manchester, United Kingdom; [12]Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan;[13]Prince of Songkla University Hospital, Songkhla, Thailand; [14]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [15]Hematology Oncology Practice Eppendorf, and University Cancer Center Hamburg, Hamburg, Germany; [16]Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; [17]Peking University Cancer Hospital & Institute; Beijing, China

Kato KN590 ESMO 2020

KEYNOTE-590 Study Design (NCT03189719)

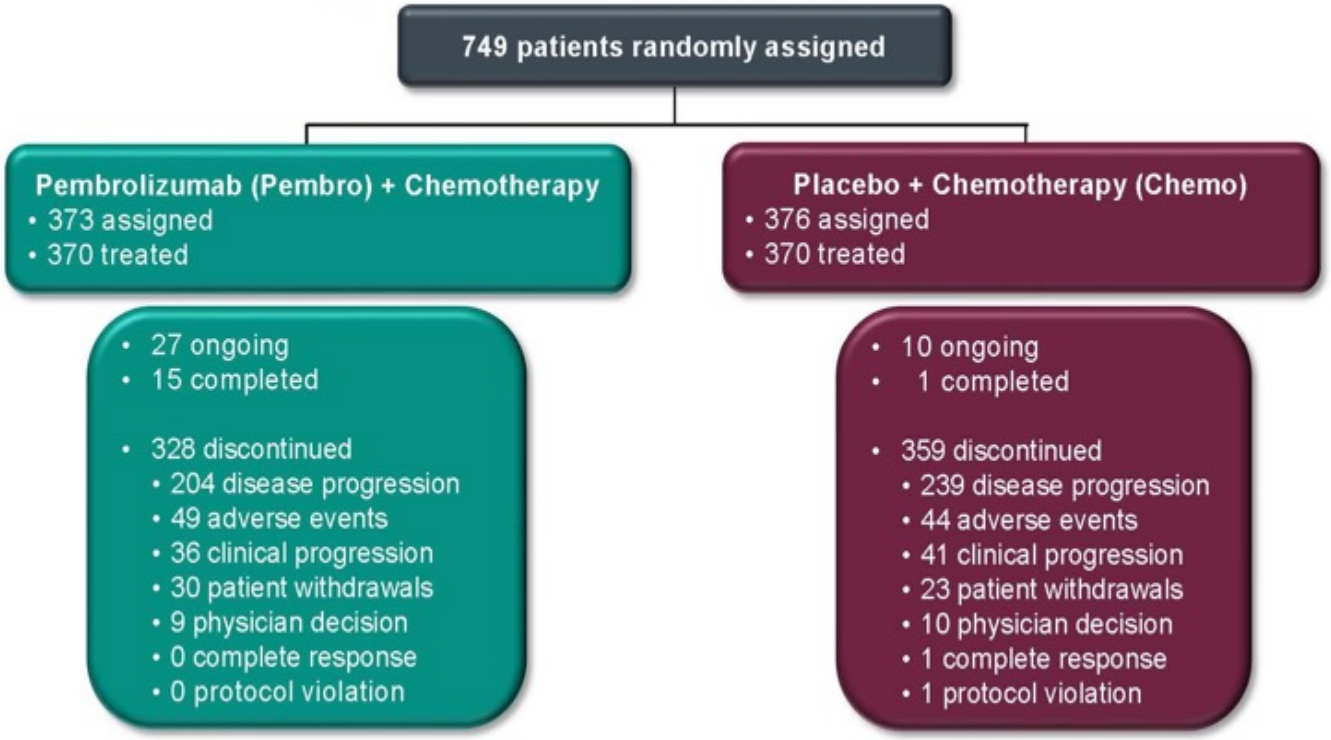


[a]Saline IV Q3W for ≤35 cycles. All treatments were continued for the specified number of cycles or until disease progression, intolerable toxicity, withdrawal of consent, or physician decision; EAC, esophageal adenocarcinoma; EGJ, esophagogastric junction, ESCC, esophageal squamous cell carcinoma.

KEYNOTE 590 ESMO 2020

Kato KN590 ESMO 2020

Treatment Disposition



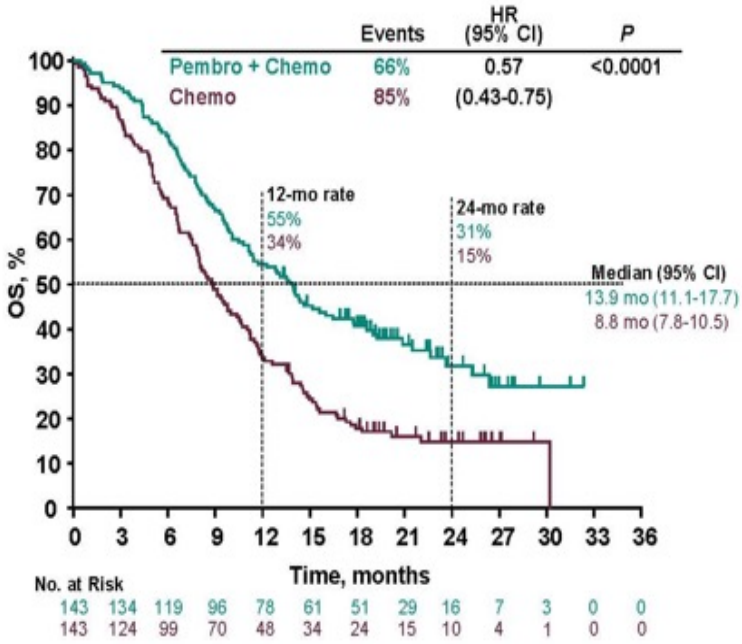
22-month recruitment period occurred from 25 Jul 2017 to 03 Jun 2019. At interim analysis median follow-up (from randomization to data cut-off or death) was 10.8 months.
Mean (SD) time on therapy was 7.7 months (6.84) vs 5.8 months (4.76) for pembro + chemo vs chemo.
43.5% vs 47.8% of patients in the pembro + chemo vs chemo group had post-study treatment; Data cutoff: July 2, 2020.

KEYNOTE 590 ESMO 2020

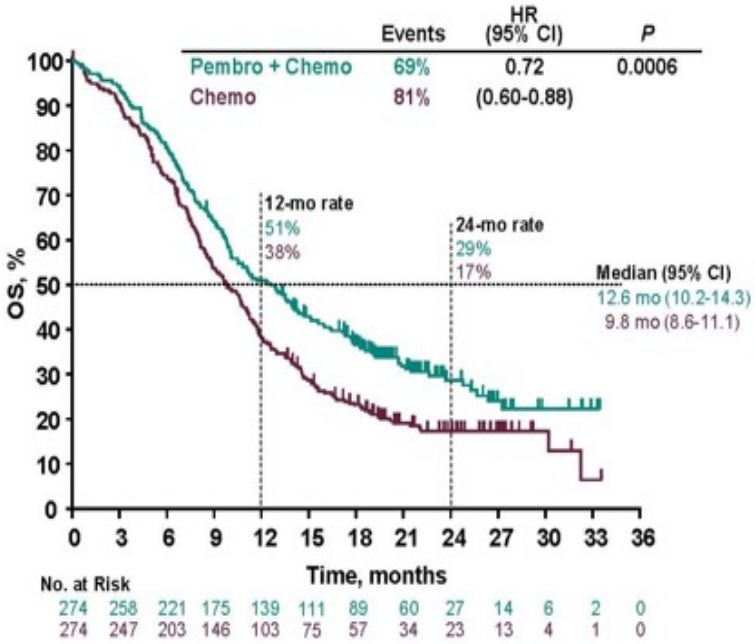
Kato KN590 ESMO 2020

Overall Survival

ESCC PD-L1 CPS ≥10



ESCC

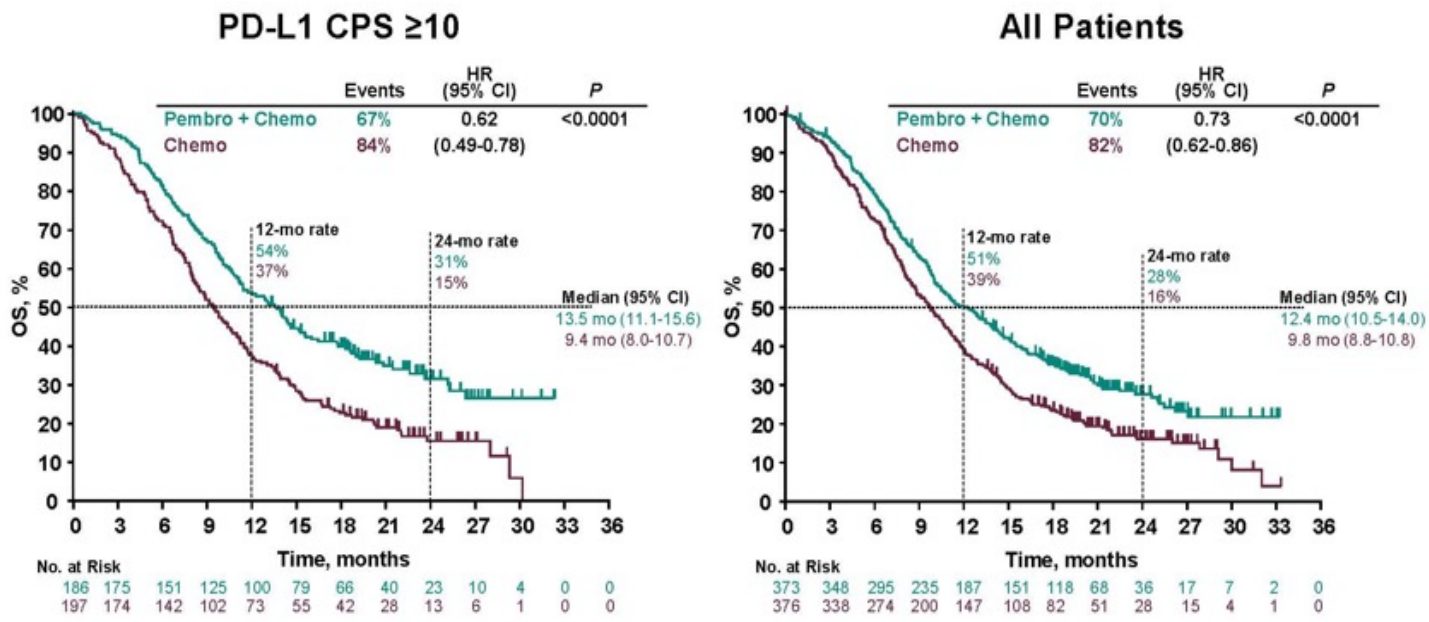


Data cut-off: July 2, 2020.

KEYNOTE 590 ESMO 2020

Kato KN590 ES

Overall Survival

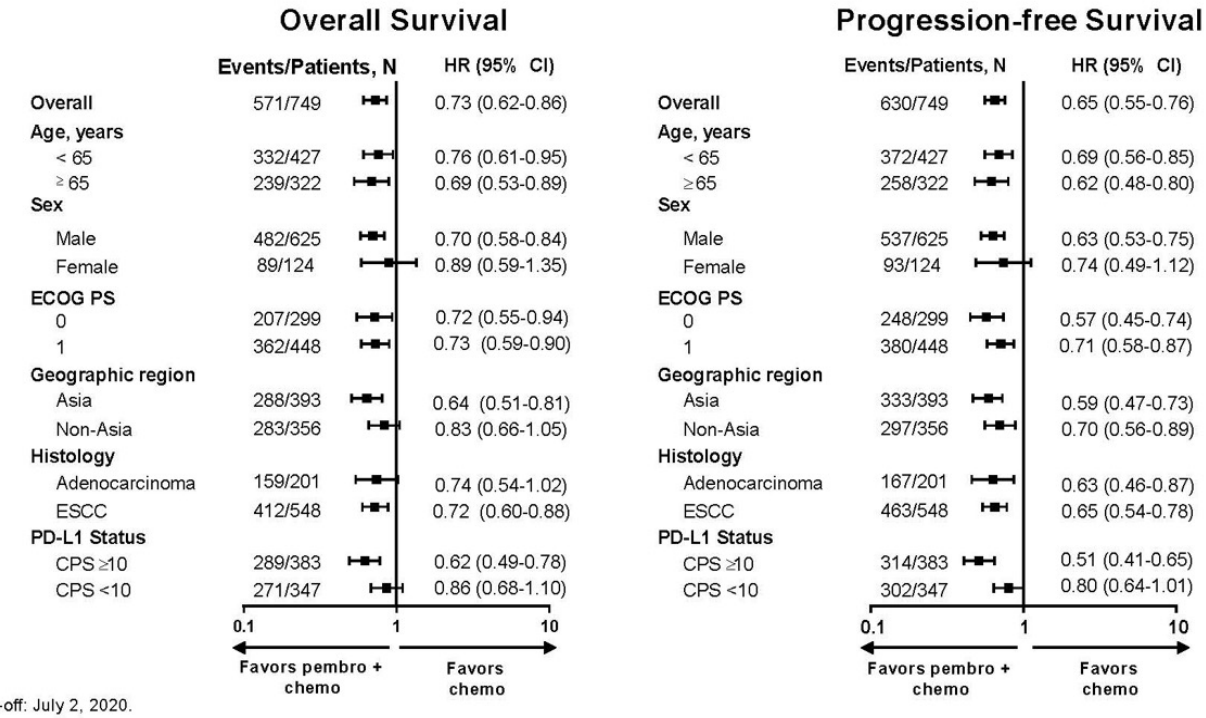


Data cut-off: July 2, 2020.

KEYNOTE 590 ESMO 2020

Kato KN590 ESMO 2020

Survival in Key Subgroups: All Patients

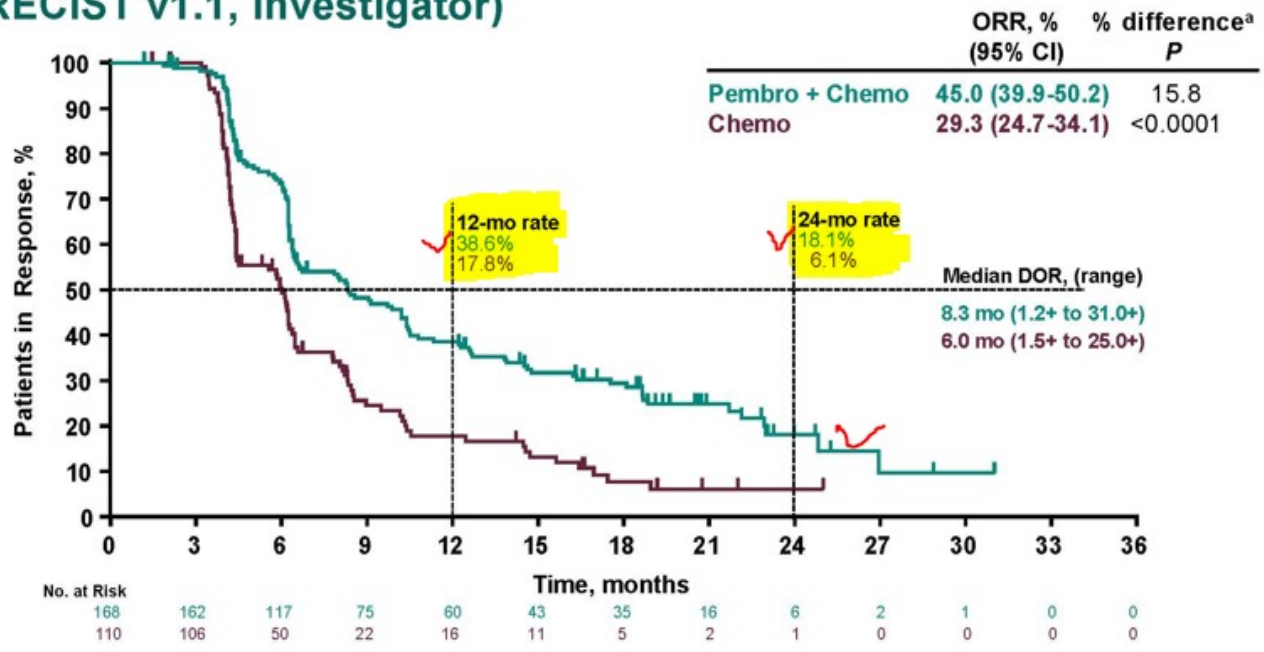


Data cut-off: July 2, 2020.

KEYNOTE 590 ESMO 2020

Kato KN590 ESMO 2020

Response Rate and Duration: All Patients
(RECIST v1.1, investigator)



[a]Estimate based on Miettinen & Nurminen method stratified by geographic region, histology, and ECOG performance status; Data cut-off: July 2, 2020.

KEYNOTE 590 ESMO 2020 conclusion

- First-line pembrolizumab plus chemotherapy vs chemotherapy plus placebo provided a statistically significant and clinically meaningful improvement in OS, PFS, and ORR in patients with locally advanced and metastatic esophageal cancer including EGJ adenocarcinoma
  - Superior OS: ESCC CPS ≥10 (HR 0.57, *P*<0.001), ESCC (HR 0.72, *P*=0.006), CPS ≥10 (HR 0.62, *P*<0.001), all patients (HR 0.73, *P*<0.001)
  - Superior PFS: ESCC (HR 0.65), CPS ≥10 (HR 0.51), all patients (HR 0.65), all *P*<0.001
  - Superior ORR: all patients (45.0% vs 29.3%, Δ15.8%, *P*<0.001)
- Comparable safety profile between the two treatment groups
  - No new safety signals detected
- Pembrolizumab plus chemotherapy should be a new standard-of-care as first-line therapy in patients with locally advanced and metastatic esophageal cancer including EGJ adenocarcinoma

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- The Treatment Paradigm of Esophageal /GE junction carcinomas is an evolving process
- The addition of Nivolumab in the adjuvant after Neoadjuvant Chemo-radiotherapy followed by Surgery led to statistically significant improvement in DFS (22 months Vs 11 months) with P= 0.003 (Checkmate 577
- Nivo + ChemoRx will represent a new standard of care in Pts with metastatic Esophageal Cancer/ GE and gastric Cancer with Median OS 14.4 Vs 11.1 Months (P=0.0001) Checkmate 649
- In the Asian Population improvement of PFS 11.45 Vs 8.34 m (Attraction4)
- Pembro + Chemo Vs ChemoRx statistically meaningful improvement in Median OS
  - ESCC → 13.9 m Vs 8.8 m (if PCS >=10) 12. 6 Vs 9.8 all PCS
  - All Esophageal cancer→ 13.5 Vs 9.4 m if PCS >=10 , 12.4 m Vs 9.8m all PCS