ESOPHAGEAL,

EGJ AND GASTRIC TUMORS

2021 PRACTICE CHANGING

J Collignon

Medical Oncology

CHU LIEGE

DISCLOSURES

ADVISORY BOARD AND LECTURES:
AMGEN,SERVIER,BAYER,MERCK,ROCHE,LILLY,SANOFY,SIRTEX,CELGENE,PFIZER,IPSEN,
NOVARTIS,BMS

(~~TRAVEL AND ACCOMODATION~~) VIRTUAL CONGRES INSCRIPTION:
ROCHE,AMGEN,PFIZER,MSD,BMS

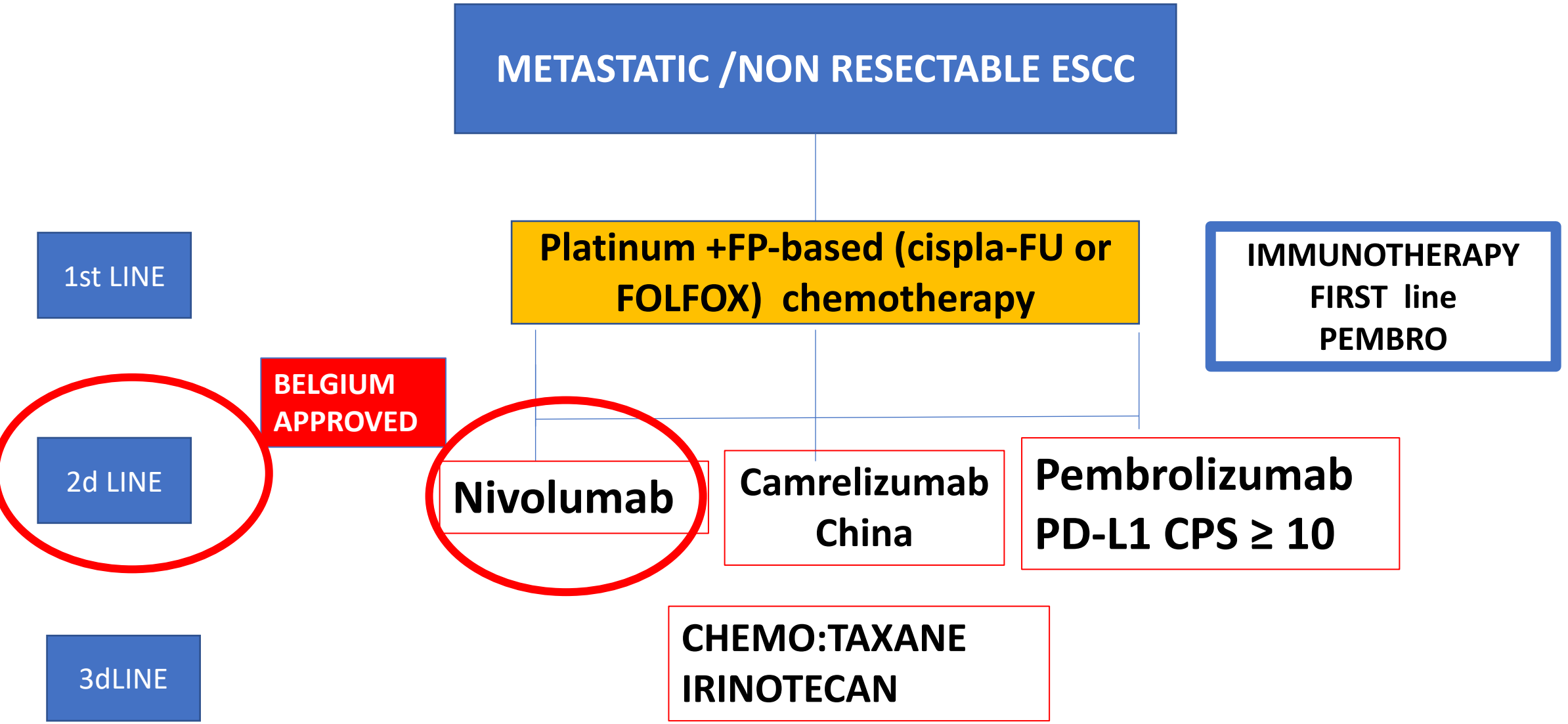
BELGIAN CANCER REGISTRY 2019:
GI CANCERS: 14 199 new cases

organ	N Males	N FEMALES	N total
Oesophagus	1212	391	1603
Gastric	540	420	960
Colon/Rectum	4300	3690	7990
Liver	804	302	1106
Gallblader+Biliary tract cancer	270	194	464
Pancreas	1041	987	2028
Anal	80	133	213

OESOGASTRIC CANCER
in BELGIUM
2021

- **SECOND LINE NIVOLUMAB FOR METASTATIC ESCC**
- First line PEMBROLIZUMAB plus chemotherapy for ESCC,ADK EC AND EGJC Sievert 1 PDL1-CPS ≥ 10
- First line NIVOLUMAB plus chemotherapy for GC EGJ ADK PDL1-CPS ≥ 5
- Adjuvant NIVOLUMAB for non pCR ESCC AND AC OESOPHAGEAL CANCER AND AC EGJC after surgery

ESCC IN 2020/21



ATTRACTION 3 ESMO 2019

N= 417

Key eligibility criteria

- **UNRESECTABLE ADVANCED OR RECURRENT ESCC**
- **REFRACTORY OR INTOLERANT OF ONE PRIOR FLUOROPYRIMIDINE/PLATINUM BASED THERAPY**
- **ECOG PS 0 OR 1**

R 1:1

NIVOLUMAB
240 mg IV Q2W

Docetaxel 75 mg/m2 IV Q3W or paclitaxel 100 mg/m2 IV QW X 6 weeks, then one week off

STRATIFICATION FACTORS

- **REGION**
- **NUMBER OF ORGANS WITH METASTASES**
- **PD-L1 expression**

primary: endpoint: OS

Other key endpoints: PFS,ORR,DCR,TTR,DOR,HRQoL and safety

ATTRACTION 3

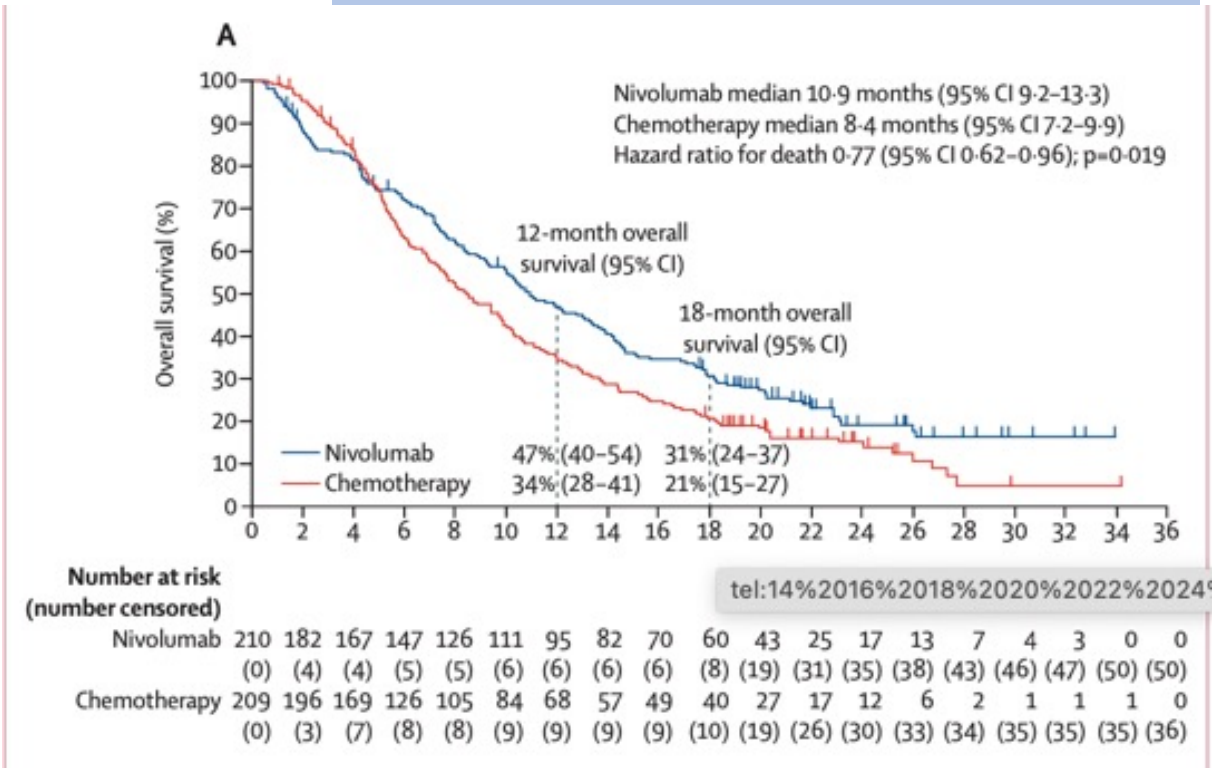
	NIVO N=210	CHEMO N=209
MEDIAN AGE years	**64**	**67**
Male %	**85**	**89**
ECOG PS %		
0	**48**	**51**
1	**52**	**49**
Race		
Asian	**96**	**96**
Caucasian	**4**	**4**
Disease stage %		
II-III	7	11
IV	88	83
Prior therapies		
Surgery	53	45
RT	73	68
Systemic anticancer therapy	100	100

Lancet Oncol 2019

Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial

Ken Kato, Byoung Chul Cho, Masanobu Takahashi, Morihito Okada, Chen-Yuan Lin, Keisho Chin, Shigenori Kadowaki, Myung-Ju Ahn, Yasuo Hamamoto, Yuichiro Doki, Chueh-Chuan Yen, Yutaro Kubota, Sung-Bae Kim, Chih-Hung Hsu, Eva Holtved, Ioannis Xynos, Mamoru Kodani, Yuko Kitagawa

Belgium approval 2021



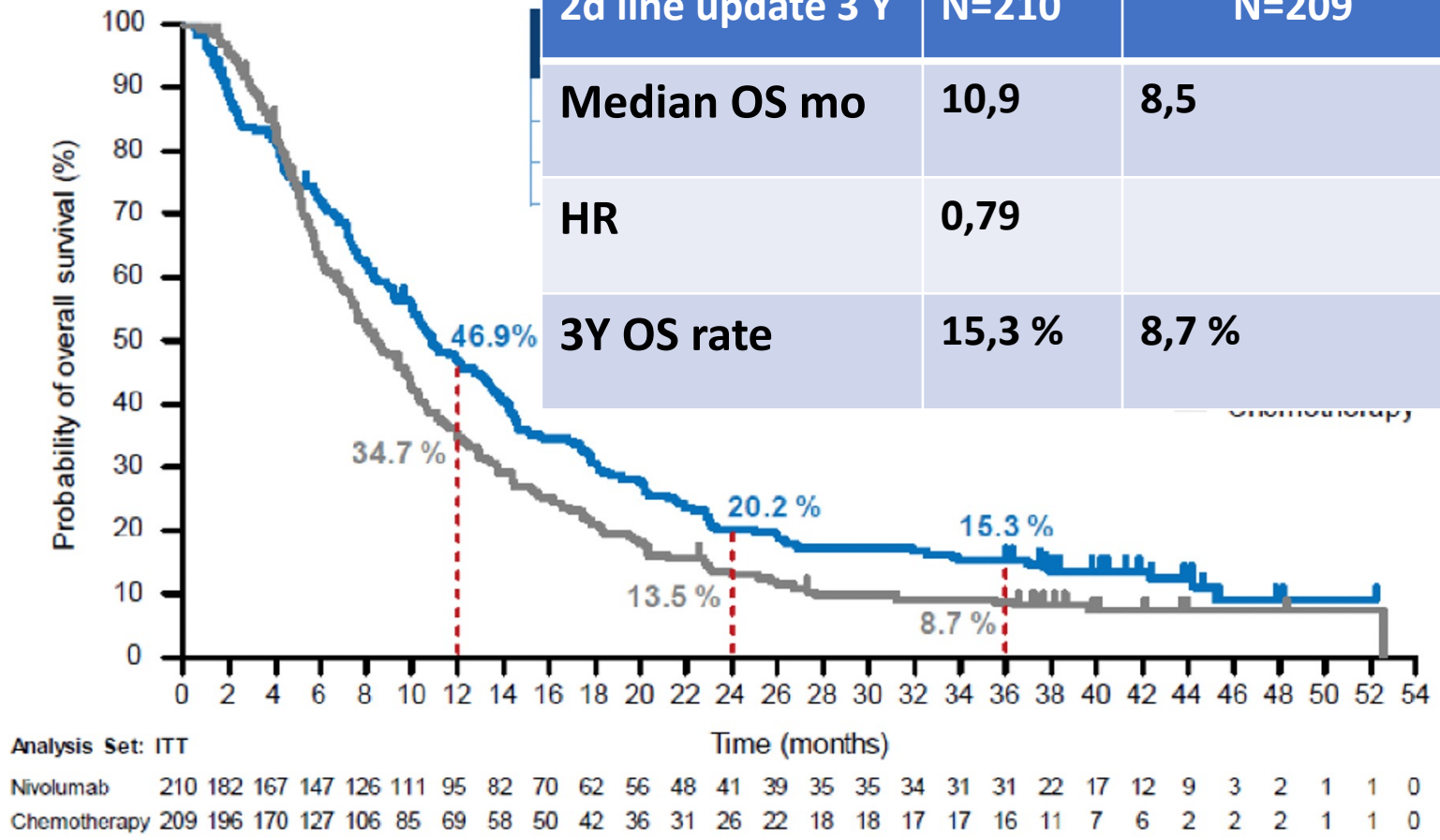
ATTRACTION-3 2d line	NIVO N=210	DOCET OR PACLI N=209
Median OS mo	10,9	8,4
HR	0,77	

Lancet Oncol 2019

ATTRACTION 3
UPDATE ASCO GI 2021

OS over three-years of follow-up

ATTRACTION-3 2d line update 3 Y	NIVO N=210	DOCET OR PACLI N=209
Median OS mo	10,9	8,5
HR	0,79	
3Y OS rate	15,3 %	8,7 %



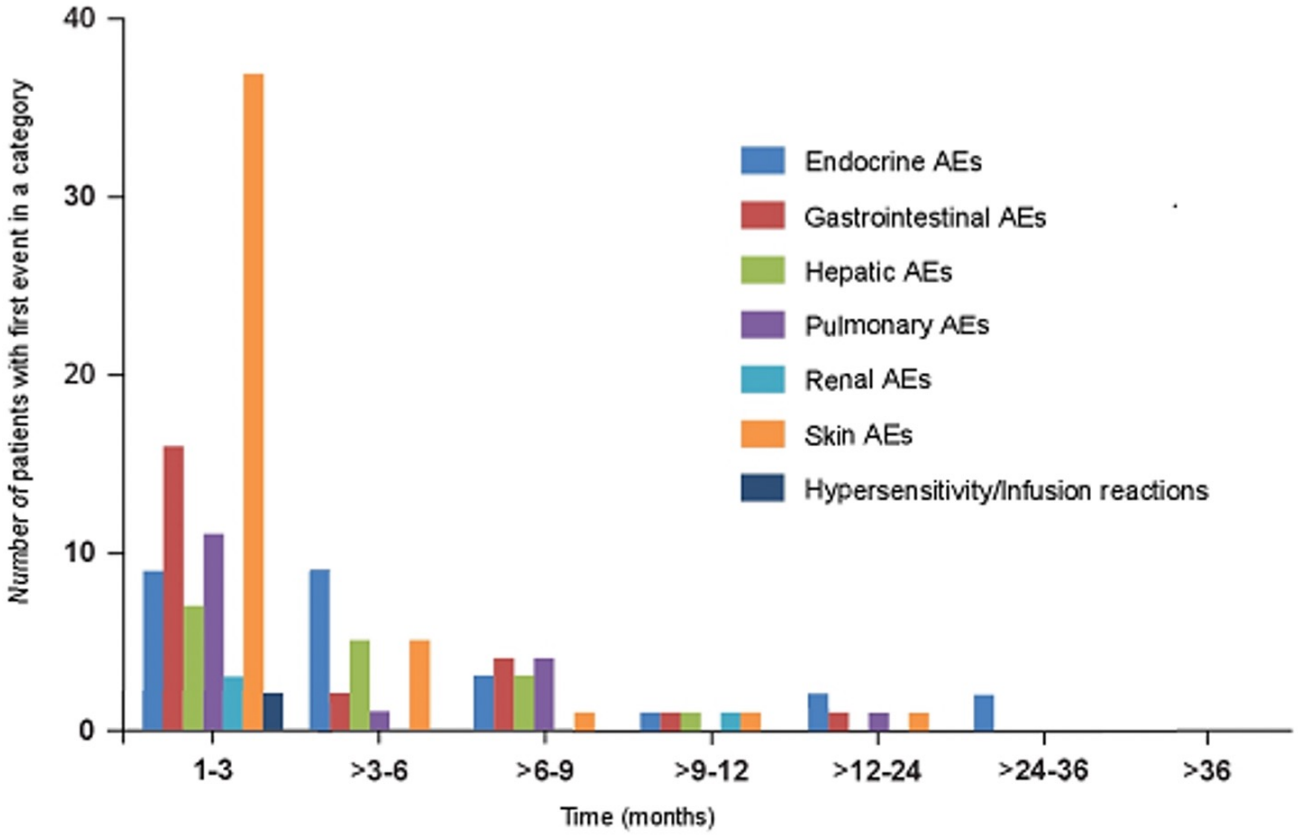
[Chin K, et al. Abstract 204

ATTRACTION 3
UPDATE ASCO GI 2021

Safety

- Most patients experienced their first select TRAE* within three months of starting nivolumab (**Figure**)
- Incidence rates of select TRAEs were comparable between 6–9 months and 1–3 years of starting nivolumab (**Figure**)
- No new safety concerns were reported during the three years of follow-up

Figure. Emergence of select TRAEs (any grade) over time



*Select TRAEs were defined as those with potential immunologic etiology that require frequent monitoring/intervention.

[Chin K, et al. Abstract 204

OESOGASTRIC CANCER
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- First line NIVOLUMAB plus chemotherapy for GC EGJ ADK PDL1-CPS ≥ 5
- Adjuvant NIVOLUMAB for non pCR ESCC AND AC OESOPHAGEAL CANCER AND AC EGJC after surgery

LOCALISATION	LOCALLY ADVANCED	METASTATIC 1 st line IMMUNOTHERAPY
ESOPHAGEAL SQUAMOUS CELL CARCINOMA		**KEYNOTE 590 (KATO,ESMO2020)** **Phase III** **Pembro + chemo(FU CISPLATIN) vs Placebo + chemo in** **Locally advanced unresectable, or metastatic EAC or ESCC** **advanced/met EGJ Siewert type 1 ADK**
ESOPHAGEAL ADENOCARCINOMA		
GASTROESOPHAGEAL JUNCTION CANCER		
GASTRIC CANCER		

PEMBRO + CHEMO FIRST LINE APPROVAL FOR ESCC, ADK EC AND EGJC Sievert 1 PDL1-CPS ≥ 10

Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study

*Jong-Mu Sun, Lin Shen, Manish A Shah, Peter Enzinger, Antoine Adenis, Toshihiko Doi, Takashi Kojima, Jean-Philippe Metges, Zhigang Li, Sung-Bae Kim, Byoung Chul Cho, Wasat Mansoor, Shau-Hsuan Li, Patrapim Sunpaweravong, Maria Alsina Maqueda, Eray Goekkurt, Hiroki Hara, Luis Antunes, Christos Fountzilas, Akihito Tsuji, Victor Castro Oliden, Qi Liu, Sukrut Shah, Pooja Bhagia, Ken Kato, on behalf of the KEYNOTE-590 Investigators**

Summary

Background First-line therapy for advanced oesophageal cancer is currently limited to fluoropyrimidine plus platinum-

Lancet 2021; 398: 759–71

KEYNOTE-590 design

Key eligibility criteria

- **Locally advanced unresectable, or metastatic EAC or ESCC or advanced/met EGJ Siewert type 1 ADK**
- **ECOG PS 0-1**
- **Treatment naive**
- **Measurable disease**

R 1:1

N=373

Pembro 200 mg IV Q3W for ≤ 35 cycles
+
Chemo 5-FU CISPLATIN Q3W for MAX 6 cycles

N=376

PLACEBO
+
Chemo 5-FU CISPLATIN Q3W for MAX 6 cycles

Stratification factors

- **ASIA vs non-ASIA region**
- **ECOG PS 0 vs 1**
- **ESCC vs EAC**

Dual primary: OS and PFS (RECIST 1.1,investigator) **in all patients** and in patients **PD-L1 expression CPS ≥ 10**
Secondary endpoints:
ORR (RECIST 1.1,investigator)
Tumor response assess at week 9 and then Q9W

Mixed histologies
Chemo with cisplatin
ASIAN around 50 %

Kato,ESMO 2020

Baseline characteristics

	PEMBRO + CHEMO N=373	CHEMO N=376
Median age years	64	62
≥ 65 Years	46	40
Male %	82	84,8
ASIAN region%	52,5	52,4
ECOG PS 1 %	59,8	59,8
Metastatic disease	92.2	90.2
Unresectable locally advanced	7,8	9,8
HISTOLOGY		
Squamous	73,5	72,9
Adenocarcinoma	26,5	27,1
Esophageal	15,5	13,8
EGJ	11	13,8
• PD-L1 expression CPS ≥ 10	49,9	52,4

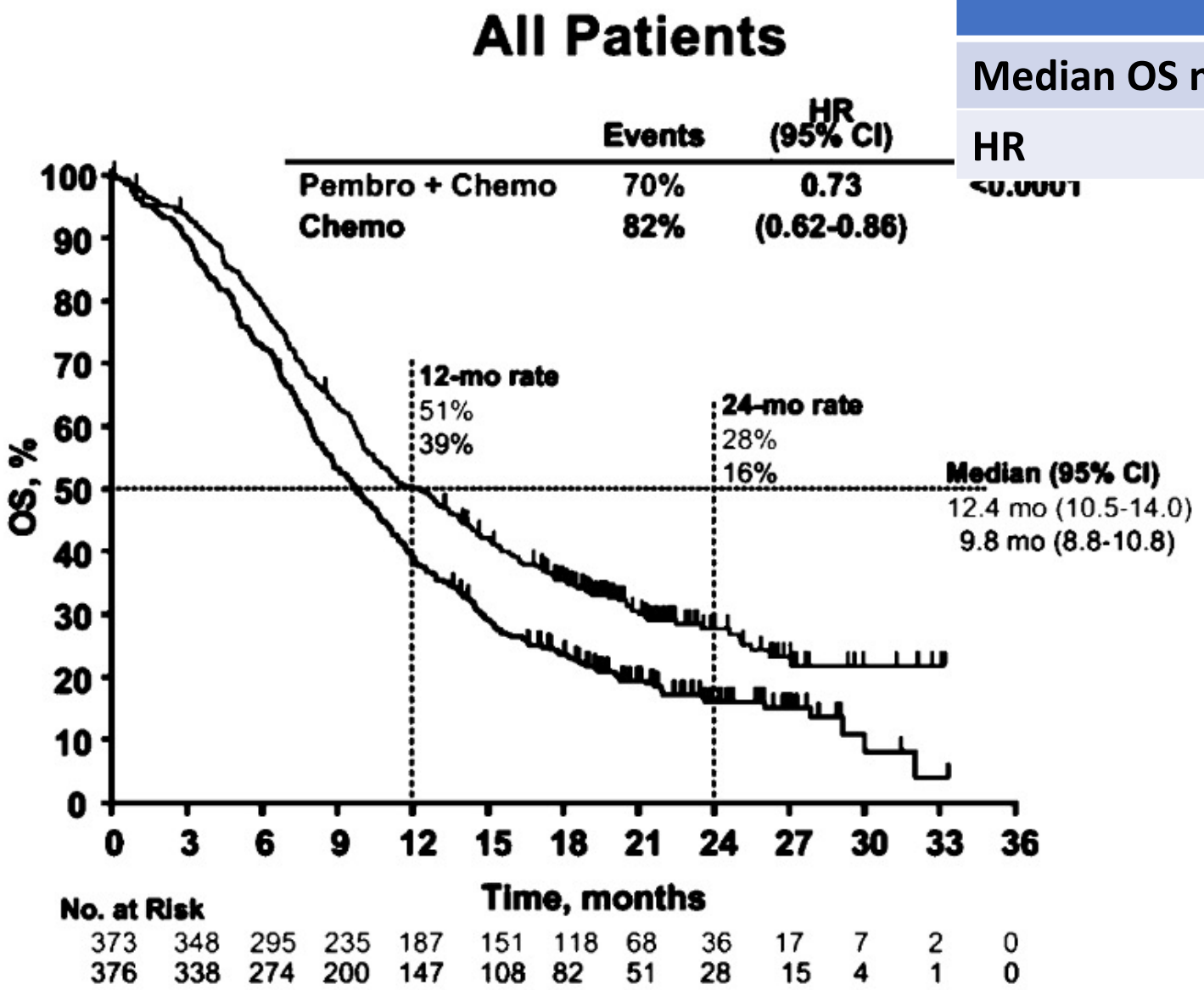
CPS=the percentage of immune cells (lymphocytes and macrophages) and tumor cells relative to the total number of viable tumor cells.

Kato,ESMO 2020

KEYNOTE-590

DUAL PRIMARY ENDPOINTS :OS;PFS

KEYNOTE-590 1st line	PEMBRO +CHEMO N= 373	PLACEBO + CHEMO N=376
Median OS mo	12,4	9,8
HR	0,73	

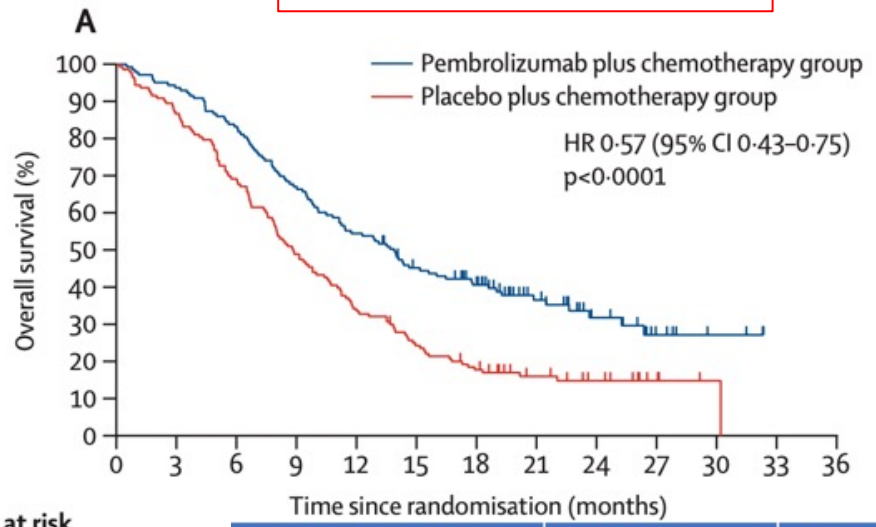


Kato,ESMO 2020

KEYNOTE-590

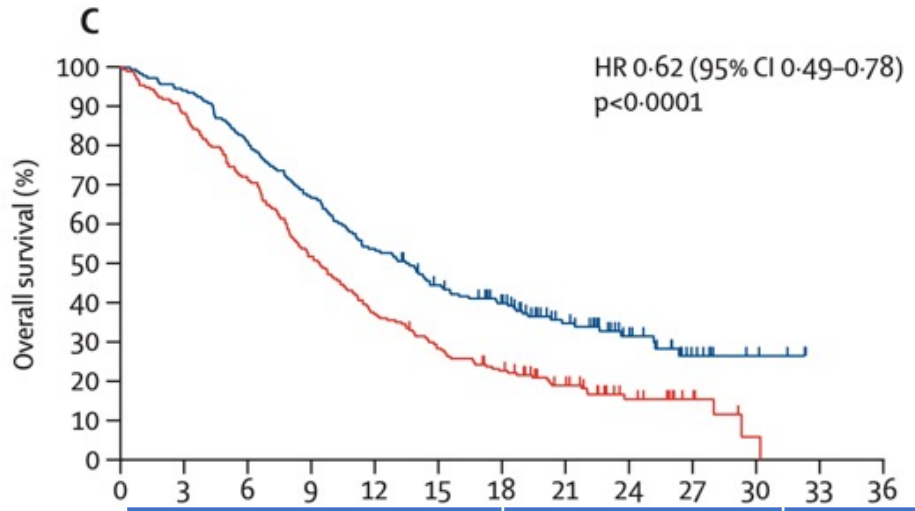
First line PEMBROLIZUMAB plus chemotherapy for ESCC,ADK EC AND EGJC Sievert 1 PDL1-CPS ≥ 10

ESCC CPS ≥ 10



KEYNOTE-590 1st line ESCC CPS ≥ 10	PEMBRO +CHEMO N= 143	PLACEBO + CHEMO N=143
Median OS mo	13,9	8,8
HR	0,57	

All patients CPS ≥ 10



KEYNOTE-590 1st line ALL CPS ≥ 10	PEMBRO +CHEMO N= 186	PLACEBO + CHEMO N=197
Median OS mo	13,5	9,4
HR	0,62	

THIS RESULTS ARE INDEPENDANT OF CPS STATUS, ALTHOUGH SQUAMOUS HISTOLOGY AND CPS ≥ 10 MAY GET A MAXIMUM BENEFIT

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LOCALISATION	LOCALLY ADVANCED	METASTATIC 1 st line IMMUNOTHERAPY
ESOPHAGEAL SQUAMOUS CELL CARCINOMA		
ESOPHAGEAL ADENOCARCINOMA		**CHECKMATE 649 (Moehler,ESMO 2020;update ASCO GI 2021;ASCO 2021,Lancet Oncology june 2021) Phase III randomised open label NIVO + CHEMO vs CHEMO In Previously untreated, unresectable, advanced or met gastric/GEJ/Oesophageal ADENOCARCINOMA** **FDA 16/4/2021**
GASTROESOPHAGEAL JUNCTION CANCER		
GASTRIC CANCER		

NIVO + CHEMO FIRST LINE
HER2 negative advanced or metastatic gastric, gastro oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a CPS ≥ 5

First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial

Yelena Y Janjigian, Kohei Shitara*, Markus Moehler, Marcelo Garrido, Pamela Salman, Lin Shen, Lucjan Wyrwicz, Kensei Yamaguchi, Tomasz Skoczylas, Arinilda Campos Bragagnoli, Tianshu Liu, Michael Schenker, Patricio Yanez, Mustapha Tehfe, Ruben Kowalyszyn, Michalis V Karamouzis, Ricardo Bruges, Thomas Zander, Roberto Pazo-Cid, Erika Hitre, Kynan Feeney, James M Cleary, Valerie Poulart, Dana Cullen, Ming Lei, Hong Xiao, Kaoru Kondo, Mingshun Li, Jaffer A Ajani*

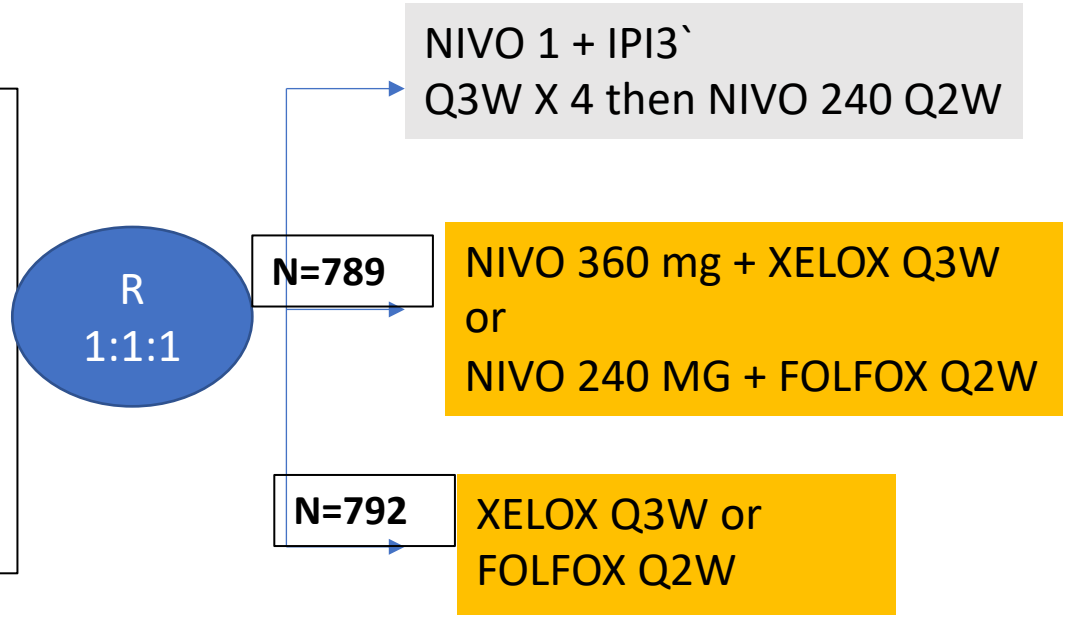
Summary

Background First-line chemotherapy for advanced or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastro-oesophageal junction adenocarcinoma has a median overall survival (OS) of less

Published Online June 5, 2021

ChekMate 649:randomised open label phase III

Key eligibility criteria
- Previously untreated,unresectable,advanced or met gastric/GEJ/Oesophageal ADK
- No known HER2 +
- ECOG PS 0-1



Minimum FU 12,1 months

Stratification factors
- Tumor cell PD-L1 expression (≥ 1 % vs < 1 %
- Region (ASIA vs US-CANADA vs ROW)
- ECOG 0 vs 1
- Chemo (xelox vs folfox)

Dual primary: OS and PFS (PD-L1 CPS ≥ 5)

Secondary endpoints:

OS (**PD-L1 CPS ≥ 1** or all randomised)

OS (**PD-L1 CPS ≥ 10**)

PFS (**PD-L1 CPS ≥ 10,1,or all randomised**)

Baseline characteristics

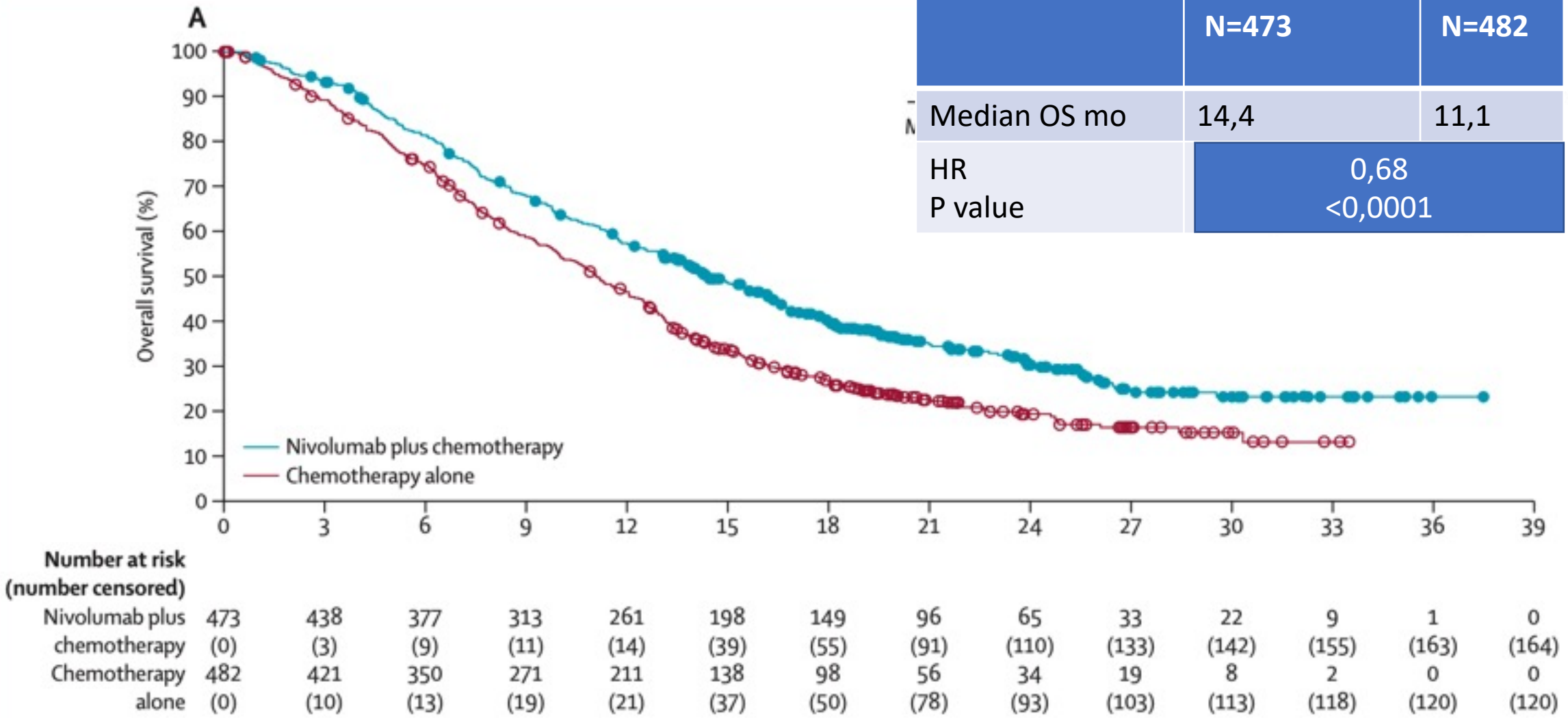
Well balanced

	PD-L1 CPS ≥ 5	
	NIVO + CHEMO (473)	CHEMO (482)
Median age years	63	62
Male %	70	72
Non-Asian/asian	75/25	76/24
ECOG PS1 %	59	58
Primary tumor location		
• GC	70	69
• GEJC	18	18
• EAC	12	13
Metastatic disease %	96	96
Liver met %	40	45
Signet ring cell carcinoma %	15	14
• MSI status %		
• MSS	89	88
• MSI-H	4	3
FOLFOX/XELOX %	51/49	52/48

Moelher,LBA6/Janjigian,Lancet oncology,2021

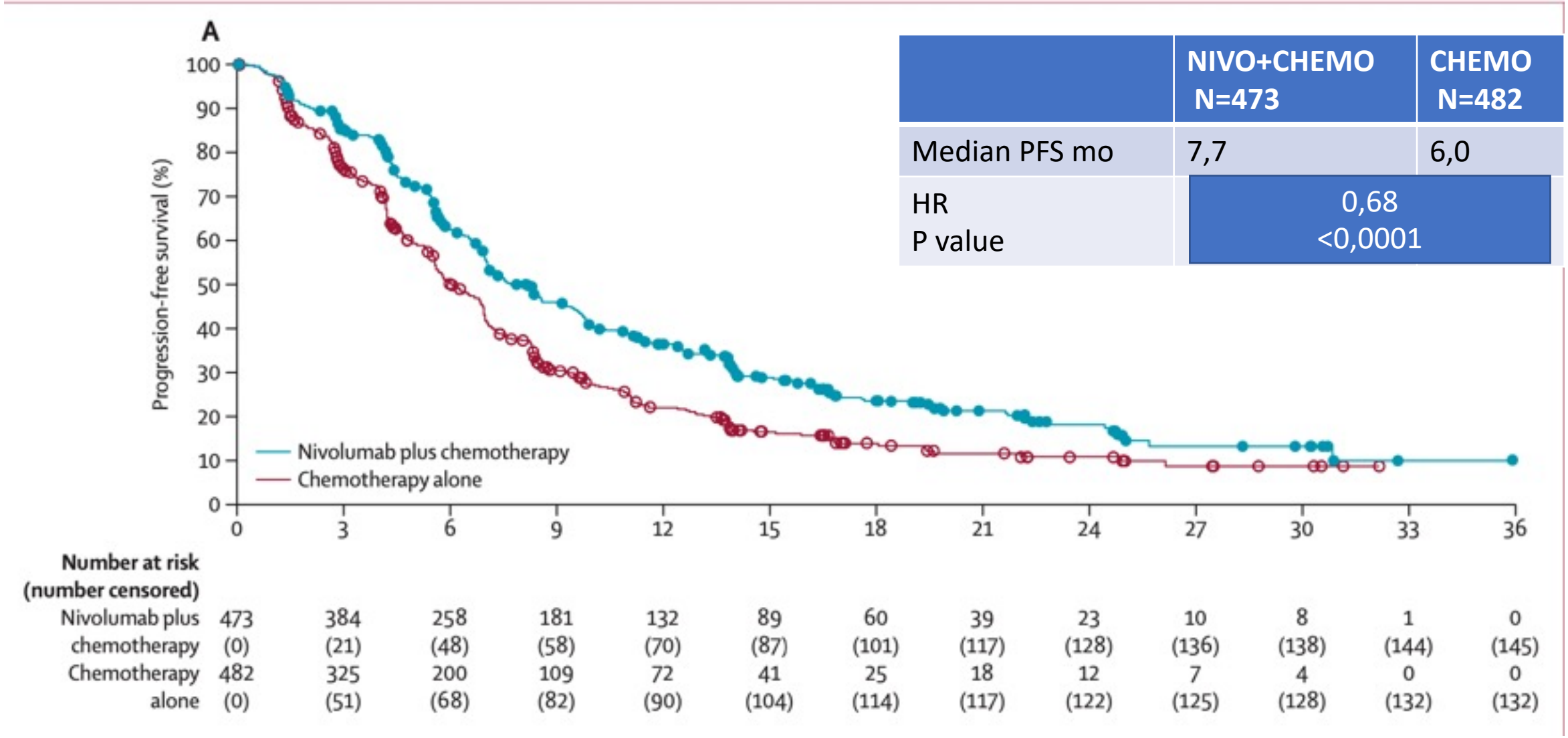
PRIMARY ENDPOINT OS (PD-L1 CPS ≥ 5)

	NIVO+CHEMO N=473	CHEMO N=482
Median OS mo	14,4	11,1
HR P value	0,68 <0,0001	



Moelher,LBA6/Janjigian,Lancet oncology,2021

PRIMARY ENDPOINT PFS (PD-L1 CPS ≥ 5)



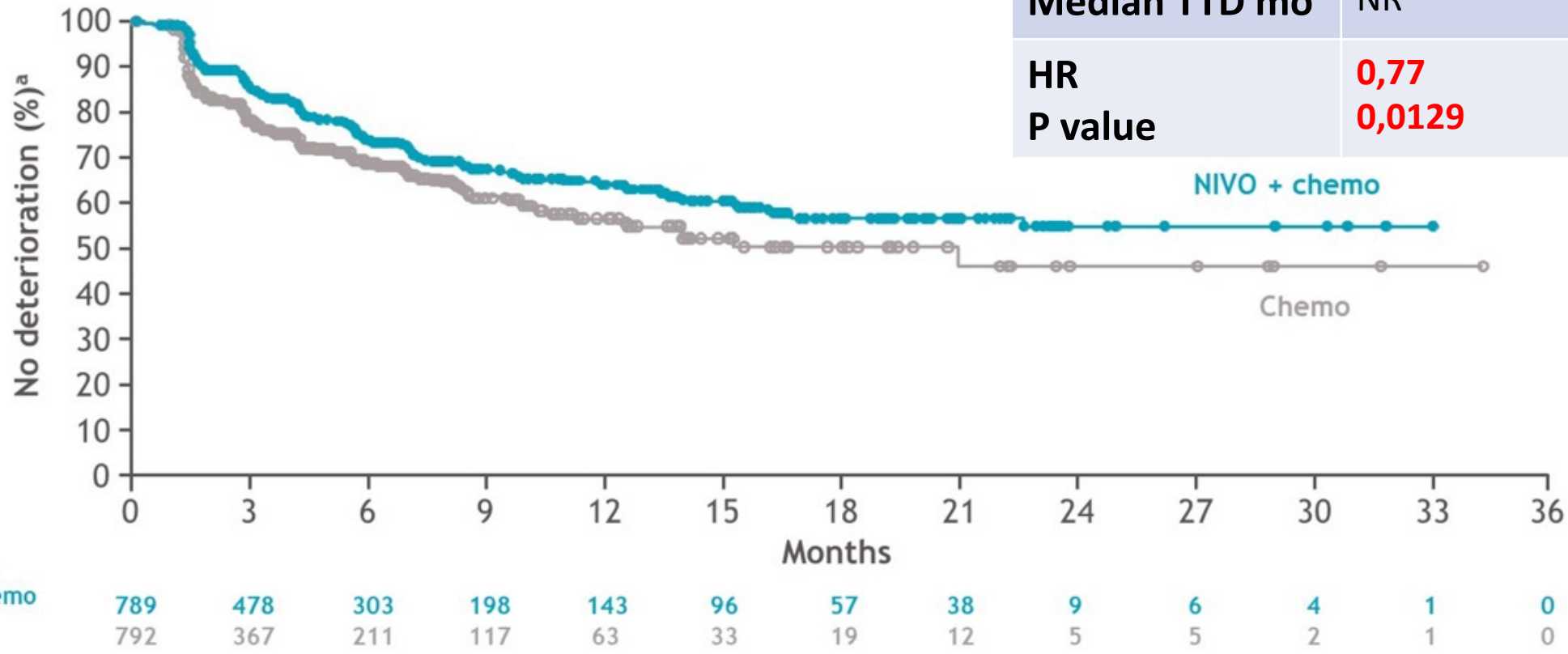
	NIVO+CHEMO N=473	CHEMO N=482
Median PFS mo	7,7	6,0
HR	0,68	
P value	<0,0001	

Moelher,LBA6/Janjigian,Lancet oncology,2021

CHECKMATE 649 UPDATE

EXPLORATORY ANALYSIS: TIME TO SYMPTOMS DETERIORATION

Checkmate 649 update All patients TTD	NIVO +CHEMO N= 789	PLACEBO + CHEMO N=792
Median TTD mo	NR	21
HR	**0,77**	
P value	**0,0129**	



Moelher, ASCO 2021,Abst 4002

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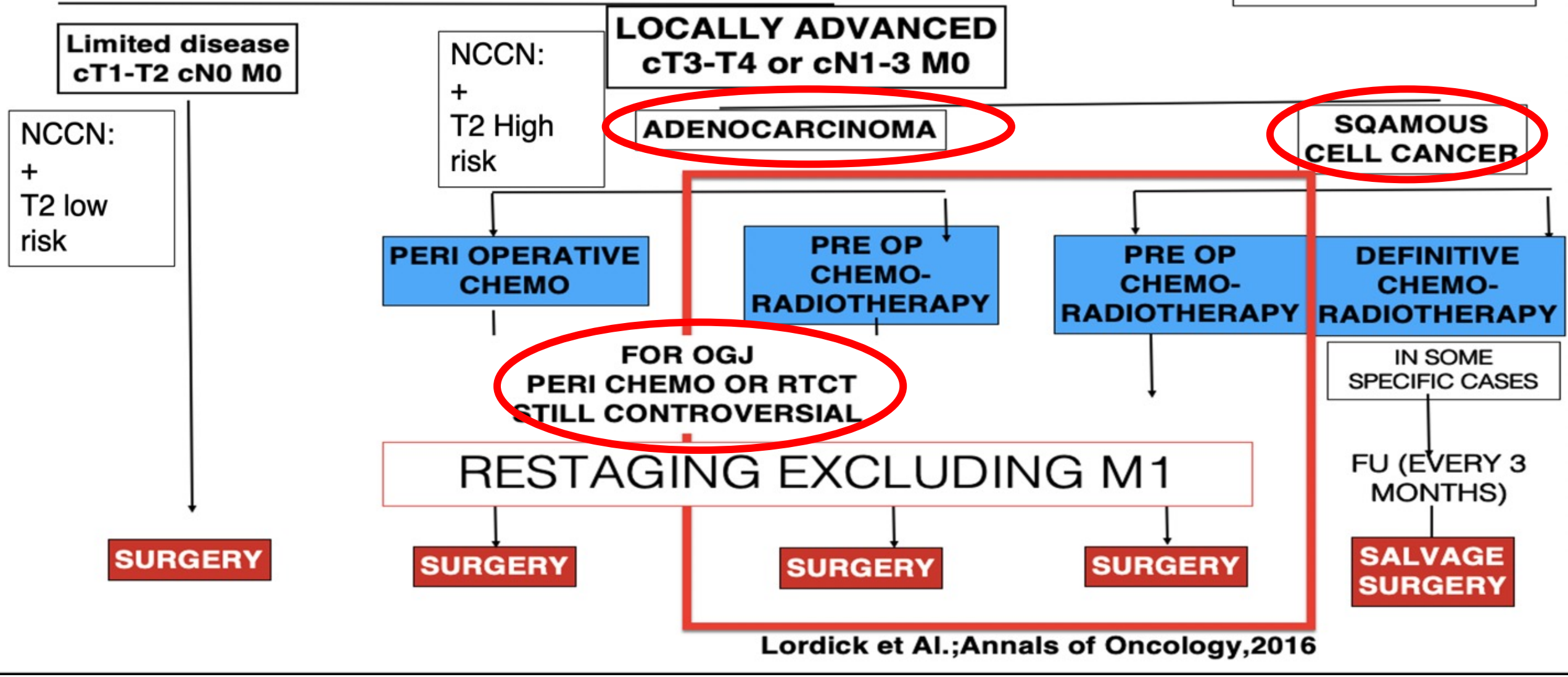
OESOPHAGEAL CANCER

ESMO 2016



Lordick et Al.;Annals of Oncology,2016

LOCALISATION	LOCALLY ADVANCED	METASTATIC 1 st line IMMUNOTHERAPY
ESOPHAGEAL SQUAMOUS CELL CARCINOMA	**CHECKMATE 577 (KELLY,ESMO 2020) Phase III** • ADC or squamous • NAD CRT + surgical resection • Residual pathologic disease≥ ypT1 or ≥ ypN1 • ECOG PS 0-1 **R 2:1: NIVOLUMAB 240 MG Q2W X 16 Weeks Then 480 MG Q4W VS PLACEBO (up to 1 year)** **N=794** **PRIMARY endpoint** **DFS**	
ESOPHAGEAL ADENOCARCINOMA		
GASTROESOPHAGEAL JUNCTION CANCER		
GASTRIC CANCER		

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 1, 2021 VOL. 384 NO. 13

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

R.J. Kelly, J.A. Ajani, J. Kuzdzal, T. Zander, E. Van Cutsem, G. Piessen, G. Mendez, J. Feliciano, S. Motoyama, A. Lièvre, H. Uronis, E. Elimova, C. Grootscholten, K. Geboes, S. Zafar, S. Snow, A.H. Ko, K. Feeney, M. Schenker, P. Kocon, J. Zhang, L. Zhu, M. Lei, P. Singh, K. Kondo, J.M. Cleary, and M. Moehler, for the CheckMate 577 Investigators*

CheckMate 577 design

Key eligibility criteria

- Stage II/III EC/GEJC
- ADC or squamous
- NAD CRT + surgical resection (R0,performed within 4-16 weeks prior to randomisation)
- Residual pathologic disease≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

R 2:1

N=794

N=532

NIVOLUMAB 240 MG
Q2W X 16 Weeks
Then 480 MG Q4W

N=262

PLACEBO
Q2W X 16 Weeks
Then Q4W

Stratification factors

- **Histology (sqamous vs ADK)**
- **Pathologis lymph nodes status (ypN1 or N0)**
- Tumor cell PD-L1 expression expression (≥ 1 % vs < 1 %)

primary:

- **DFS**

Secondary endpoints:

- **OS**
- **OS rate at 1,2 and 3 year**

Kelly,LBA9

Baseline characteristics

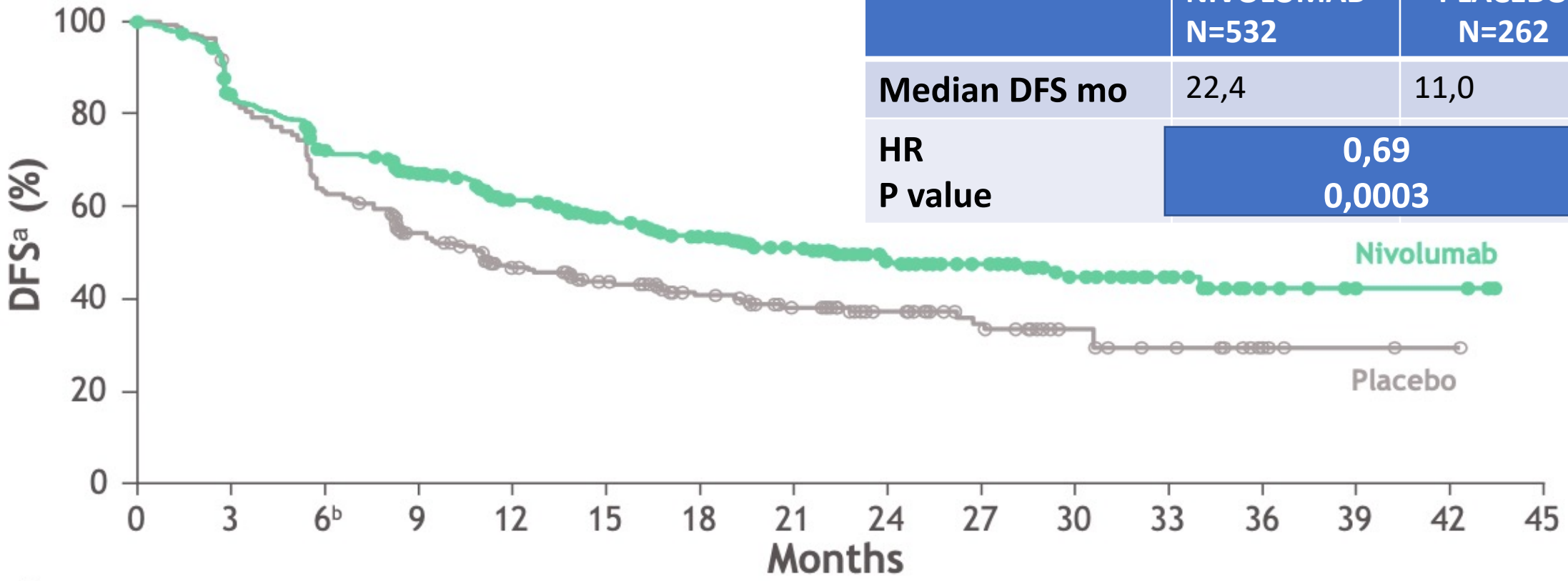
	NIVOLUMAB N=532	PLACEBO N=262
Median age years	62	61
Male %	84	85
RACE %		
White	81	82
Asian	16	13
ECOG PS 0/1 %	58/42	60/40
Disease stage at initial diagnosis II/III %	34/66	38/62
Tumor location		
EC	60	59
GEJC	40	41
HISTOLOGY %		
Squamous	29	29
Adenocarcinoma	71	71
Pathologic lymph node status ≥ ypN1 %	57	58
• PD-L1 expression		
• ≥ 1 %	17	15
• < 1 %	70	75
• Indeterminate/non evaluable	13	10

Kelly,LBA9

FIRST POSITIVE TRIAL IN ADJUVANT SINCE CROSS AND FLOT TRIAL

PRIMARY ENDPOINT DFS

	NIVOLUMAB N=532	PLACEBO N=262
Median DFS mo	22,4	11,0
HR	0,69	
P value	0,0003	



No. at risk

Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

[a]Per investigator assessment; [b]6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; [c]The boundary for statistical significance at the pre-specified interim analysis required the *P* value to be less than 0.036.

Kelly,LBA9

CheckMate 577 design
SAFETY

Event	Nivolumab (N = 532)		Placebo (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Any adverse event†	510 (96)	183 (34)	243 (93)	84 (32)
Serious adverse event	158 (30)	107 (20)	78 (30)	53 (20)
Adverse event leading to discontinuation of trial regimen	68 (13)	38 (7)	20 (8)	16 (6)
Any adverse event related to nivolumab or placebo†‡	376 (71)	71 (13)	119 (46)	15 (6)
Serious adverse event related to nivolumab or placebo‡	40 (8)	29 (5)	7 (3)	3 (1)
Related adverse event leading to discontinuation of trial regimen‡	48 (9)	26 (5)	8 (3)	7 (3)

NIVOLUMAB WAS WELL TOLERATED AND MAJORITY OF TRAES WERE GRADE 1 OR 2

Kelly,NEJM 2021

CheckMate 577 design
SAFETY

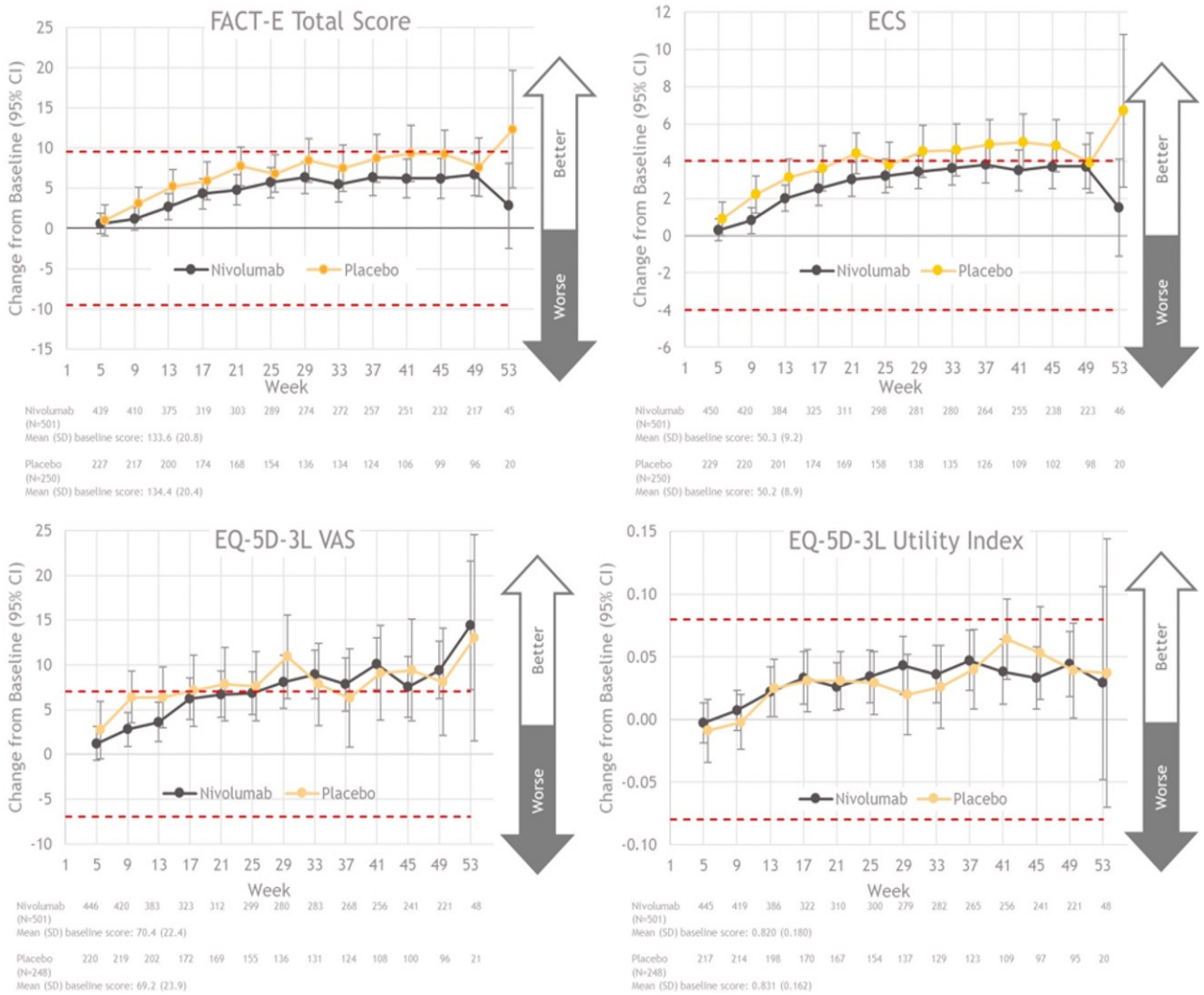
Mean HRQoL scores at baseline were similar between
treatment groups (**Figure**)
A statistically significant difference was observed between nivolumab and placebo groups for ECS and Trial Outcome Index (both of which favored placebo)

- However, these differences were not clinically meaningful

Time to first deterioration of HRQoL was not found to be statistically significant between nivolumab and placebo

- No significant differences were seen for subgroup analyses

Figure. Mean change in PRO scores over time



Abstract 167 Van Cutsem ASCO GI 2021

CONCLUSIONS

Immunotherapy in Oesogastric cancer

4 PRACTICES CHANGING THIS YEAR IN BELGIUM

TRIAL	CHECKMATE-649 L1	KEYNOTE 590 L1	Checkmate 577 adjuvant
DISEASE location	GC, EGJ ,Esophagus	Esophagus ,EGJ sievert 1	Esophagus, EGJ
Histology	ADK	ADK/SCC	ADK/SCC
Region	Global	Global	Global
PFS HR	0,68 CPS ≥ 5	0,62 CPS ≥ 10	0,69
ORR	45 vs 60 % (CPS ≥ 5)	30 vs 48 %	NA
OS difference	3,3 m (CPS ≥ 5) 2,7 m (CPS ≥ 1) 2,2 All patients	5,1 m ESCC CPS ≥ 10) 2,8 m ESCC	NR but DFS X2
ESMO MCBS (Magnitude of Clinical Benefit Scale)	4 (CPS ≥ 5) 3 (CPS ≥ 1) 2 (all patients)	4 ESCC (CPS ≥ 10) 3 vs 4 all ESCC 3 vs 4 all pats	Grade A

Modified from Smyth, Annals of Oncology 2021

BELGIUM APPROVALS

ESOPHAGEAL OR EGJ ADK	ESOPHAGEAL SQUAMOUS CELL CARCINOMA
LOCALLY ADVANCED ESOPHAGEAL OR EGJ ADK CRT+ SURGERY **NO PCR:ADJUVANT NIVOLUMAB**	LOCALLY ADVANCED CRT+ SURGERY **NO PCR:ADJUVANT NIVOLUMAB**
1L METASTATIC **NIVO + CHEMO (CPS ≥ 5) FOR GC ALSO** **PEMBRO + CHEMO (CPS ≥ 10) NOT FOR GC** **CHEMO + Tmab (HER2+)** **CHEMO ALONE (HER2- CPS <5)**	1L METASTATIC **PEMBRO + CHEMO (CPS ≥ 10)**
2L METASTATIC **TAXANE +/- RAMUCIRUMAB OR IRINOTECAN**	2L METASTATIC **NIVOLUMAB**
3-4 L METASTATIC **TRIFLURIDIN-TIPIRACIL OR IRINOTECAN OR BSC**	3-4L METASTATIC **TAXANE OR IRINOTECAN OR BSC**

INSTITUT JULES BORDET

ONCODISTINCT NETWORK

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J Collignon
CHU LIEGE
Medical Oncology

The highest grades of the **ESMO-MCBS** in the curative setting are A and B and in the non-curative setting 5 and 4, which indicate a substantial magnitude of clinical benefit.