nature portfolio

https://doi.org/10.1038/s41586-022-04508-4

Supplementary information

Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer

In the format provided by the authors and unedited

SI Guide

Supplemental information to

Nivolumab plus chemotherapy or ipilimumab in gastroesophageal cancer

Shitara K, Ajani JA, Markus Moehler M, et al.

Corresponding author:

Yelena Y Janjigian, MD
Gastrointestinal Oncology Service, Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, NY
Phone number: (+)1-646-888-4286
janjigiy@mskcc.org

Table of Contents

1. List of Sites and Investigators 2
Principal investigators for each site who participated in this trial 2
2. Supplemental Tables 6
Supplemental Table 1 | Baseline demographics and clinical characteristics in all randomized patients 6
Supplemental Table 2 | Subsequent therapies 8
Supplemental Table 3 | Duration of treatment in all treated patients 9
Supplemental Table 4 | Summary of treatment-related adverse events and events with potential immunologic etiology in all treated patients 10
3. Patient-Reported Outcomes 12

1. LIST OF SITES AND INVESTIGATORS

Principal investigators for each site who participated in this trial

Argentina	Luciana Bellaquero
	Diego Kaen
	Ruben Kowalyszyn
	Guillermo Mendez
	Juan Manuel O'Connor
	Felipe Palazzo
	Eduardo Richardet
Australia	Sumitra Ananda
	Geoffrey Chong
	Kynan Feeney
	Andrew Hill
	Craig Kukard
	Adnan Nagrial
	Arvind Sahu
	Nimit Singhal
Brazil	Anelisa Araujo
	Maria Ignez Braghiroli
	Arinilda Campos Bragagnoli
	Sergio de Azevedo
	Fabio Franke
Canada	Jean-Sebastien Aucoin
	Felix Couture
	Elena Elimova
	Petr Kavan
	Frederic Lemay
	Mustapha Tehfe
	Mark Vincent
	Xiaofu Zhu
Chile	Olga Barajas
	Marcelo Garrido
	Eugenia Loredo Fort
	Pamela Salman
	Patricio Yanez
China	Yi Ba
	Chunmei Bai
	Li Bai
	Yuxian Bai
	Ying Cheng
	Weijian Guo
	Wenwei Hu
	Wei Li
	Xiaoyan Lin

	Tianshu Liu
	Jianwei Lu
	Hongming Pan
	Shukui Qin
	Lin Shen
	Yong Tang
	Jufeng Wang
	Nong Xu
	Ruihua Xu
	Nong Yang
	Jingdong Zhang
	Xiaochun Zhang
	Haijun Zhong
Colombia	Ricardo Bruges
	Carlos Narvaez
	Carlos Ortiz
Czech Republic	Zdenek Kral
	Jiri Tomasek
France	Romain Cohen
	Farid el Hajbi
	Pierre-Luc Etienne
	Ludovic Evesque
	Marie-Pierre Galais
	Francois Ghiringhelli
	Emmanuelle Samalin
	Yann Touchefeu
Germany	Heiko Becker
	Gunnar Folprecht
	Stefan Kasper-Virchow
	Verena Keitel
	Sylvie Lorenzen
	Markus Moehler
	Marianne Sinn
	Peter Thuss-Patience
	Thomas Zander
Greece	Gerasimos Aravantinos
	Haralabos Kalofonos
	Michalis Karamouzis
	George Pentheroudakis
Hong Kong	Ka On Lam
	Winnie Yeo
Hungary	Peter Arkosy
	Magdolna Dank
	Erika Hitre
Israel	Baruch Brenner

	Ravit Geva
	Ayala Hubert
	Maria Passhak
	Einat Shacham Shmueli
Italy	Michele Basso
	Alfredo Falcone
	Gabriele Luppi
	Evaristo Maiello
	Mario Mandala
	Vincenzo Montesarchio
Japan	Hiroki Hara
	Ken Kato
	Yoshito Komatsu
	Keiko Minashi
	Yukiya Narita
	Taroh Satoh
	Kohei Shitara
	Toshimi Takano
	Akihito Tsuji
	Kensei Yamaguchi
Mexico	Adriana Dominguez Andrade
	Angel Gomez Villanueva
	Alejandro Juarez Ramiro
Peru	Ashley Alarcon
	Paola Montenegro
	Renzo Salas
	Hermes Tejada
Poland	Iwona Drab-Mazur
	Tomasz Skoczylas
	Lucjan Wyrwicz
Portugal	Antonio Quintela
	Nuno Sousa
Romania	Adina Croitoru
	Filip Dumitru
	Doina Elena Ganea
	Anca Mihailov
	Michael Schenker
Russia	Larisa Bolotina
	Oleg Gladkov
	Nina Karaseva
	Elena Poddubskaya
	Sergey Tjulandin
Singapore	Chau Hsien Matthew Ng
	Wei-Peng Yong
South Korea	Hyun Cheol Chung

	Yoon Koo Kang
Spain	Maria Alsina
	Cristina Buges
	Andres Cervantes
	Ignacio Delgado
	Jose Federico Gonzalez
	Roberto Antonio Pazo Cid
Taiwan	Yee Chao
	Jen-Shi Chen
Turkey	Irfan Cicin
	Hasan Coskun
	Ali Kaplan
	Mehmet Ali Nahit Sendur
	Dogan Uncu
UK	Ian Chau
	Tim Iveson
	Srinivasan Madhusudan
	Wasat Mansoor
USA	Jaffer Ajani
	Ari Baron
	Johanna Bendell
	David Chang
	James Cleary
	Allen Cohn
	Jay Courtright
	Sarah Davis
	Joseph Fiorillo
	Sunil Gandhi
	Henrik Bo Illum
	Syma Iqbal
	Yelena Janjigian
	Blair Jobe
	Alok Khorana
	Kristen Marrone
	Steven McCune
	Andrew Scott Paulson
	James Reeves
	Joel Saltzman
	Usman Shah
	Richard Siegel
	Antonio Ucar
	Victoria Villaflor
	Benjamin Weinberg

2. SUPPLEMENTAL TABLES

Supplemental Table 1 | Baseline demographics and clinical characteristics in all randomized patients

	Nivolumab plus chemotherapy (*n* = 789)[a]	Chemotherapy (*n* = 792)[a]	Nivolumab plus ipilimumab (*n* = 409)[b]	Chemotherapy (*n* = 404)[b]
Age (years), median (range)	62 (18–88)	61 (21–90)	62 (22–84)	61 (23–90)
<65	473 (60)	488 (62)	258 (63)	251 (62)
≥65	316 (40)	304 (38)	151 (37)	153 (38)
Sex, *n* (%)				
Male	540 (68)	560 (71)	278 (68)	280 (69)
Female	249 (32)	232 (29)	131 (32)	124 (31)
Race, *n* (%)				
Asian	186 (24)	189 (24)	124 (30)	121 (30)
White	556 (70)	541 (68)	264 (65)	263 (65)
Other[c]	47 (6)	62 (8)	21 (5)	20 (5)
Region, *n* (%)				
Asia	178 (23)	178 (22)	118 (29)	117 (29)
USA and Canada	131 (17)	132 (17)	75 (18)	69 (17)
Rest of the world	480 (61)	482 (61)	216 (53)	218 (54)
ECOG PS,[d] *n* (%)				
0	326 (41)	336 (42)	180 (44)	185 (46)
1	462 (59)	452 (57)	228 (56)	219 (54)
Primary tumor location at initial diagnosis, *n* (%)				
Gastric cancer	554 (70)	556 (70)	282 (69)	282 (70)
GEJ cancer	132 (17)	128 (16)	82 (20)	73 (18)
Esophageal adenocarcinoma	103 (13)	108 (14)	45 (11)	49 (12)
Tumor cell PD-L1 expression, *n* (%)				
<1%[e]	663 (84)	664 (84)[f]	341 (83)	337 (83)
≥1%	126 (16)	127 (16)	68 (17)	67 (17)
Previous surgery, *n* (%)				
Yes	160 (20)	176 (22)	86 (21)	95 (24)
No	629 (80)	616 (78)	323 (79)	309 (76)
Organs with metastases, *n* (%)				
1	164 (21)	183 (23)	83 (20)	100 (25)
≥2	602 (76)	583 (74)	326 (80)	304 (75)
Liver metastases,[g] *n* (%)				
Yes	301 (38)	314 (40)	149 (36)	160 (40)
No	465 (59)	452 (57)	255 (62)	228 (56)
Signet ring cell carcinoma,[h] *n* (%)				
Yes	145 (18)	136 (17)	71 (17)	83 (21)
No	644 (82)	656 (83)	338 (83)	321 (79)
Lauren's classification, *n* (%)				
Intestinal type	272 (34)	267 (34)	134 (33)	119 (29)
Diffuse type	254 (32)	273 (34)	143 (35)	160 (40)
Mixed	58 (7)	48 (6)	20 (5)	28 (7)
Unknown	205 (26)	204 (26)	112 (27)	97 (24)
Microsatellite instability status,[i] *n* (%)				
MSS	695 (88)	682 (86)	355 (87)	344 (85)
MSI-H	23 (3)	21 (3)	11 (3)	10 (2)
Chemotherapy regimen,[j] *n* (%)				
FOLFOX	422/782 (54)	406/767 (53)	NA	181/389 (47)
CapeOX	360/782 (46)	361/767 (47)	NA	208/389 (53)
Albumin, *n* (%)				
<LLN	179 (23)	178 (22)	89 (22)	74 (18)

≥LLN	578 (73)	581 (73)	311 (76)	316 (78)
Not reported	32 (4)	33 (4)	9 (2)	14 (3)
Previous adjuvant or neoadjuvant therapy, *n* (%)				
Adjuvant	63 (8)	56 (7)	22 (5)	31 (8)
Neoadjuvant	48 (6)	61 (8)	27 (7)	33 (8)
Metastatic disease	1 (<1)	0	0	0
Disease stage, *n* (%)				
Metastatic	757 (96)	756 (95)	391 (96)	386 (96)
Locally advanced	27 (3)	34 (4)	14 (3)	18 (4)
Locally recurrent	5 (1)	2 (<1)	4 (1)	0
PD-L1 CPS expression, *n* (%)				
<1	140 (18)	125 (16)	80 (20)	77 (19)
≥1	641 (81)	656 (83)	322 (79)	319 (79)
<5	308 (39)	299 (38)	168 (41)	157 (39)
≥5	473 (60)	482 (61)	234 (57)	239 (59)
<10	406 (51)	389 (49)	221 (55)	198 (50)
≥10	375 (48)	392 (49)	181 (45)	198 (50)
Not evaluable/ indeterminate/missing	8 (1)	11 (1)	7 (2)	8 (2)
Site of metastases, *n* (%)				
Liver	301 (38)	314 (40)	149 (36)	160 (40)
Peritoneum	188 (24)	188 (24)	95 (23)	98 (24)
CNS	1 (<1)	0	0	0

[a]Concurrently randomized in nivolumab plus chemotherapy versus chemotherapy; [b]Concurrently randomized in nivolumab plus ipilimumab versus chemotherapy; [c]Included American Indian or Alaska Native (nivolumab plus chemotherapy versus chemotherapy, *n* = 26; nivolumab plus ipilimumab versus chemotherapy, *n* = 3), Black or African American (nivolumab plus chemotherapy versus chemotherapy, *n* = 18; nivolumab plus ipilimumab versus chemotherapy, *n* = 9) and not reported (nivolumab plus chemotherapy versus chemotherapy, *n* = 1); [d]Based on case report form. ECOG PS of 2 was reported in four patients in the nivolumab plus chemotherapy versus chemotherapy group and one patient in the nivolumab-plus-ipilimumab versus chemotherapy group. ECOG PS was not reported for one patient in the nivolumab plus chemotherapy versus chemotherapy group. All randomly assigned patients had ECOG PS of 0 or 1 based on interactive response technology; [e]Includes indeterminate tumor cell PD-L1 expression; [f]One patient had missing PD-L1 expression at baseline; [g]Liver metastases not reported for 49 patients in the nivolumab plus chemotherapy versus chemotherapy group and 21 patients in the nivolumab plus ipilimumab versus chemotherapy group; [h]Per WHO histological classification; [i]MSI status was not reported or invalid for 160 patients in the nivolumab plus chemotherapy versus chemotherapy group and 93 patients in the nivolumab plus ipilimumab versus chemotherapy group; [j]Patients who received at least one dose of the assigned treatment. CapeOX, capecitabine plus oxaliplatin; CNS, central nervous system; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX, 5-fluorouracil plus leucovorin plus oxaliplatin; GEJ, gastroesophageal junction; LLN, lower limit of normal; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NA, not applicable; PD-L1, programmed death ligand 1.

Supplemental Table 2 | Subsequent therapies

	Nivolumab plus chemotherapy (*n* = 789)	Chemotherapy (*n* = 792)	Nivolumab plus ipilimumab (*n* = 409)	Chemotherapy (*n* = 404)
Any subsequent therapy[a]	325 (41)	346 (44)	196 (48)	187 (46)
Subsequent radiotherapy	43 (5)	48 (6)	26 (6)	25 (6)
Subsequent surgery	20 (3)	26 (3)	13 (3)	11 (3)
Subsequent systemic anti-cancer therapy	290 (37)	329 (42)	186 (45)	179 (44)
Most frequent systemic anti-cancer therapies				
Chemotherapy	281 (36)	306 (39)	179 (44)	167 (41)
Taxanes				
Paclitaxel	165 (21)	185 (23)	58 (14)	105 (26)
Docetaxel	20 (3)	23 (3)	15 (4)	18 (4)
Fluoropyrimidine-based chemotherapy				
Fluorouracil	78 (10)	108 (14)	119 (29)	57 (14)
Capecitabine	28 (4)	25 (3)	28 (7)	14 (3)
Fluoropyrimidine	0	2[b] (<1)	–	–
Platinum-based chemotherapy				
Oxaliplatin	32 (4)	29 (6)	146 (36)	29 (7)
Carboplatin	9 (1)	10 (1)	6 (1)	7 (2)
Cisplatin	15 (2)	17 (2)	10 (2)	14 (3)
Targeted therapy				
Ramucirumab	101 (13)	96 (12)	29 (7)	65 (16)
Apatinib	13 (2)	21 (3)	7 (2)	16 (4)
Immunotherapy	17 (2)	73 (9)	11 (3)	47 (12)
Nivolumab	10 (1)	35 (4)	6 (1)	28 (7)
Pembrolizumab	3 (<1)	29 (4)	4 (1)	18 (4)
Atezolizumab	0	4 (<1)	–	–
Toripalimab	1 (<1)	3 (<1)	0	1 (<1)
Ipilimumab	1 (<1)	2 (<1)	0	1 (<1)
Other	3 (<1)	3 (<1)	2 (<1)	1 (<1)

Data are presented as *n* (%). [a]Patients could have received more than one type of therapy; [b]Includes one patient who received floxuridine.

CheckMate 649 Manuscript Revision

Supplemental Table 3 | Duration of treatment in all treated patients

Treatment	Median duration of treatment, months (range)	Dose reduction or omission, *n* (%)
Nivolumab plus chemotherapy (*n* = 782)	6.8 (0.1–45.0)	–
Nivolumab plus CapeOX (*n* = 360)		
Nivolumab[a] (mg)	5.5 (0.0–24.1)	–
Oxaliplatin[b] (mg/m^2)	4.0 (0.0–23.2)	167 (46)
Capecitabine[c] (mg/m^2)	5.7 (0.1–45.0)	53 (15)
Nivolumab plus FOLFOX (*n* = 422)		–
Nivolumab[a] (mg)	6.7 (0.0–26.0)	–
Oxaliplatin[b] (mg/m^2)	4.6 (0.0–23.5)	181 (43)
5-Fluorouracil bolus[b] (mg/m^2)	5.3 (0.0–35.2)	140 (33)
5-Fluorouracil continuous[b] (mg/m^2)	5.9 (0.1–35.2)	181 (43)
Chemotherapy (*n* = 767)	4.9 (0.0–44.2)	–
CapeOX (*n* = 361)		
Oxaliplatin[b] (mg/m^2)	3.7 (0.0–34.4)	145 (40)
Capecitabine[c] (mg/m^2)	4.8 (0.0–44.2)	56 (16)
FOLFOX (*n* = 406)		
Oxaliplatin[b] (mg/m^2)	4.2 (0.0–35.4)	181 (45)
5-Fluorouracil bolus[b] (mg/m^2)	4.4 (0.0–42.9)	148 (37)
5-Fluorouracil continuous[b] (mg/m^2)	4.9 (0.1–42.9)	152 (37)
Nivolumab plus ipilimumab (*n* = 403)	1.9 (0.0–24.1)	–
Nivolumab[a] (mg)	2.5 (0.7–24.5)	–
Ipilimumab[a] (mg)	1.4 (0.0–5.0)	–
Chemotherapy	4.9 (0.1–45.5)	–
CapeOX (*n* = 208)	4.9 (0.1–44.2)	–
Oxaliplatin[b] (mg/m^2)	3.8 (0.0–34.4)	91 (44)
Capecitabine[c] (mg/m^2)	4.9 (0.1–44.2)	41 (20)
FOLFOX (*n* = 181)	4.7 (0.1–45.5)	–
Oxaliplatin[b] (mg/m^2)	4.1 (0.0–35.4)	83 (46)
5-Fluorouracil bolus[b] (mg/m^2)	4.3 (0.0–45.4)	66 (37)
5-Fluorouracil continuous[b] (mg/m^2)	4.7 (0.1–45.5)	69 (38)

[a]Dose reductions were not allowed for nivolumab or ipilimumab; [b]Includes patients with at least one dose reduction; [c]Includes patients with at least one omitted dose. FOLFOX, 5-fluorouracil plus leucovorin plus oxaliplatin; CapeOX, capecitabine plus oxaliplatin.

Supplemental Table 4 | Summary of treatment-related adverse events and events with potential immunologic etiology in all treated patients

	Nivolumab plus chemotherapy (*n* = 782)[a,b]		Chemotherapy (*n* = 767)[a,b]		Nivolumab plus ipilimumab (*n* = 403)[a,c]		Chemotherapy (*n* = 389)[a,c]	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Events in 10% or more of treated patients in either group								
Nausea	328 (42)	21 (3)	300 (39)	19 (2)	38 (9)	6 (1)	179 (46)	16 (4)
Diarrhea	258 (33)	35 (4)	207 (27)	24 (3)	72 (18)	11 (3)	112 (29)	15 (4)
Neuropathy peripheral	225 (29)	33 (4)	193 (25)	22 (3)	3 (<1)	1 (<1)	93 (24)	9 (2)
Anemia	205 (26)	47 (6)	173 (23)	20 (3)	30 (7)	5 (1)	85 (22)	9 (2)
Fatigue	206 (26)	30 (4)	174 (23)	18 (2)	64 (16)	11 (3)	85 (22)	8 (2)
Vomiting	198 (25)	17 (2)	170 (22)	24 (3)	22 (5)	4 (1)	86 (22)	11 (3)
Neutropenia	193 (25)	121 (15)	185 (24)	96 (13)	6 (1)	1 (<1)	93 (24)	44 (11)
Decreased appetite	158 (20)	14 (2)	139 (18)	13 (2)	41 (10)	5 (1)	89 (23)	6 (2)
Neutrophil count decreased	159 (20)	84 (11)	118 (15)	67 (9)	5 (1)	1 (<1)	69 (18)	40 (10)
Thrombocytopenia	159 (20)	21 (3)	149 (19)	14 (2)	6 (1)	1 (<1)	70 (18)	7 (2)
Platelet count decreased	158 (20)	20 (3)	115 (15)	19 (2)	6 (1)	2 (<1)	59 (15)	11 (3)
Peripheral sensory neuropathy	137 (18)	16 (2)	119 (16)	14 (2)	1 (<1)	0	54 (14)	6 (2)
Aspartate aminotransferase increased	123 (16)	13 (2)	70 (9)	5 (<1)	53 (13)	16 (4)	36 (9)	2 (<1)
White blood cell count decreased	114 (15)	23 (3)	77 (10)	13 (2)	4 (1)	0	52 (13)	9 (2)
Alanine aminotransferase increased	90 (12)	7 (<1)	51 (7)	5 (<1)	52 (13)	16 (4)	27 (7)	1 (<1)
Palmar-plantar erythrodysaesthesia syndrome	97 (12)	12 (2)	83 (11)	8 (1)	0	0	47 (12)	2 (<1)
Lipase increased	89 (11)	45 (6)	34 (4)	16 (2)	45 (11)	28 (7)	21 (5)	11 (3)
Rash	77 (10)	7 (<1)	12 (2)	0	59 (15)	10 (2)	8 (2)	0
Asthenia	76 (10)	7 (<1)	83 (11)	10 (1)	28 (7)	2 (<1)	34 (9)	5 (1)
Hypothyroidism	71 (9)	0	2 (<1)	0	48 (12)	0	2 (<1)	0
Amylase increased	71 (9)	21 (3)	22 (3)	2 (<1)	42 (10)	18 (4)	15 (4)	3 (<1)
Pyrexia	64 (8)	4 (<1)	22 (3)	1 (<1)	42 (10)	1 (<1)	12 (3)	0
Events with potential immunologic etiology in all treated patients[a,d]								
Endocrine	109 (14)	6 (<1)	3 (<1)	0	89 (22)	15 (4)	2 (<1)	0
Gastrointestinal	266 (34)	43 (5)	208 (27)	25 (3)	84 (21)	26 (6)	113 (29)	16 (4)
Hepatic	207 (26)	31 (4)	138 (18)	17 (2)	104 (26)	47 (12)	74 (19)	9 (2)
Pulmonary	41 (5)	14 (2)	4 (<1)	1 (<1)	15 (4)	4 (1)	1 (<1)	0
Renal	29 (4)	7 (<1)	9 (1)	2 (<1)	17 (4)	6 (1)	6 (2)	1 (<1)
Skin	218 (28)	27 (3)	108 (14)	8 (1)	146 (36)	17 (4)	55 (14)	2 (<1)

Data are presented as *n* (%). [a]Patients who received at least one dose of the assigned treatment. Includes events reported between first dose and 30 days after last dose of trial therapy. Treatment-relatedness in the nivolumab plus chemotherapy group refers to nivolumab, at least one chemotherapy

component or both and in the nivolumab plus ipilimumab group to nivolumab, ipilimumab or both. National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and Medical Dictionary for Regulatory Activities, version 23.0; [b]Concurrently randomized to nivolumab plus chemotherapy versus chemotherapy; [c]Concurrently randomized to nivolumab plus ipilimumab versus chemotherapy; [d]Treatment-related select adverse events by organ category that have potential immunologic etiology and require frequent monitoring/intervention.

3. PATIENT-REPORTED OUTCOMES

Among patients with PD-L1 CPS ≥5 and all-randomized patients who were eligible for PRO assessments, the proportion completing the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) questionnaire in both treatment arms was 90% or more at baseline and 80% or more at most subsequent assessments for which at least 10 patients were eligible (until week 133). Mean total scores at baseline were similar between the nivolumab-plus-chemotherapy and chemotherapy alone groups in PD-L1 CPS ≥5 and all-randomized patients.[1]

Reference

1. Janjigian, Y. Y. et al. 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. *Lancet* **398**, 27-40 (2021).