The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

A CME/MOC- and NCPD-Accredited Event

Saturday, October 22, 2022
7:30 AM – 5:30 PM ET

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — Lung Cancer: *Drs Langer and Lovly*

Module 2 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs LaCasce and Smith*

Module 3 — Prostate and Bladder Cancers: *Drs Morgans and Yu*

Module 4 — Renal Cell Carcinoma: *Prof Powles*

Module 5 — Multiple Myeloma: *Dr Usmani*

Module 6 — Hepatobiliary Cancers: *Prof Abou-Alfa*

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Agenda

Module 7 — Breast Cancer: *Drs Goetz and Krop*

Module 8 — Endometrial Cancer: *Dr Westin*

Module 9 — Ovarian Cancer and PARP Inhibitors: *Dr O'Malley*

Module 10 — Gastrointestinal Cancers: *Drs Messersmith and Strickler*

Module 11 — Melanoma: *Prof Long*

Gastrointestinal Cancers Faculty

Wells A Messersmith, MD
Chief Medical Officer, Cancer Center
Associate Director of Clinical Services
University of Colorado Cancer Center
Aurora, Colorado

John Strickler, MD
Associate Professor
Duke University
Durham, North Carolina

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Colorectal Cancer (CRC)

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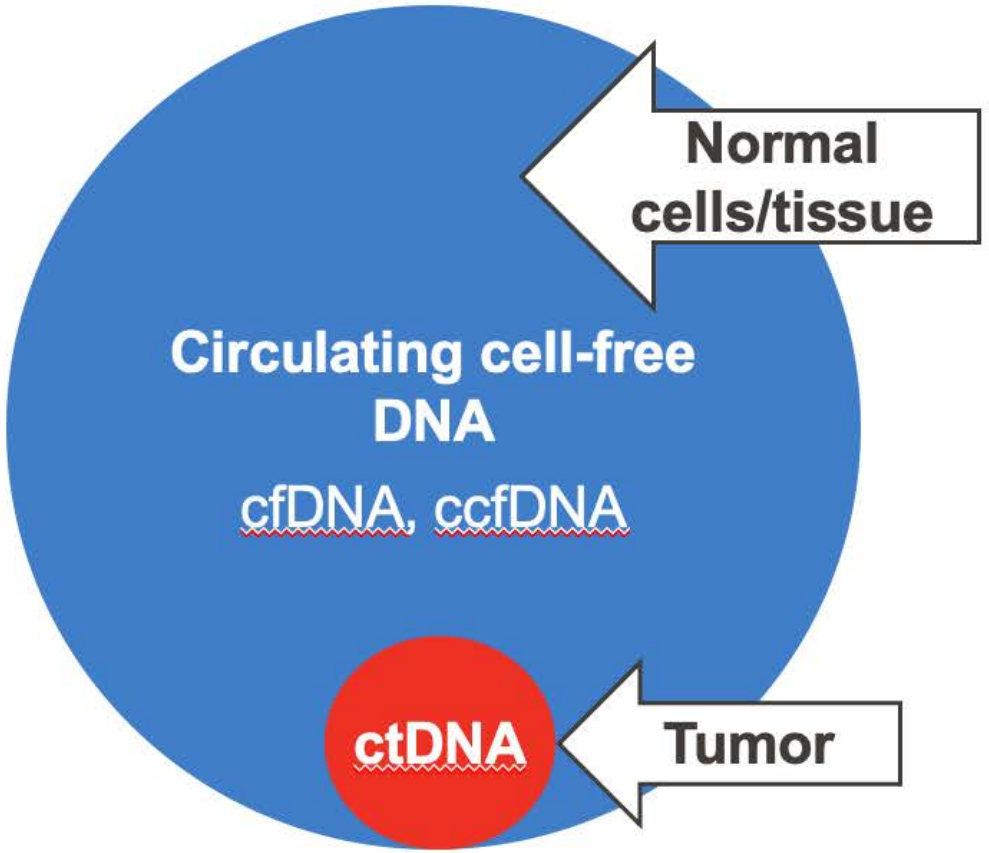
Characteristics and Terminology for Circulating Tumor DNA (ctDNA)



Initially described by Madel and Metais in 1948
Half-life: ~ 0.5 hours

Two Main Ways to Test ctDNA:

- "Tumor-informed testing"
  - Sequencing the tumor and looking for those mutations
- "Tumor-naïve testing"
  - Casting a wide net and looking for tumor mutations

Chandrananda D et al. *BMC Med Genomics.* 2015;8:29; Wyllie AH. *Nature.* 1980;284(5756):555-556; Mandel P & Metais P. *C R*

Content courtesy of Christopher Lieu, MD

CONSENSUS STATEMENT

OPEN

Check for updates

ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal–Anal Task Forces whitepaper

Arvind Dasari[1,40]✉, Van K. Morris[1,40], Carmen J. Allegra[2], Chloe Atreya[3], Al B. Benson III[4], Patrick Boland[5], Ki Chung[6], Mehmet S. Copur[7], Ryan B. Corcoran[8], Dustin A. Deming[9], Andrea Dwyer[10], Maximilian Diehn[11], Cathy Eng[1], Thomas J. George[12], Marc J. Gollub[13], Rachel A. Goodwin[14], Stanley R. Hamilton[15], Jaclyn F. Hechtman[16], Howard Hochster[17], Theodore S. Hong[18], Federico Innocenti[19], Atif Iqbal[20], Samuel A. Jacobs[21], Hagen F. Kennecke[22], James J. Lee[23], Christopher H. Lieu[24], Heinz-Josef Lenz[25], O. Wolf Lindwasser[26], Clara Montagut[27], Bruno Odisio[28], Fang-Shu Ou[29], Laura Porter[30], Kanwal Raghav[1], Deborah Schrag[31], Aaron J. Scott[32], Qian Shi[29], John H. Strickler[33], Alan Venook[34], Rona Yaeger[35], Greg Yothers[36], Y. Nancy You[37], Jason A. Zell[38,39] and Scott Kopetz[1]

Nat Rev Clin Oncol 2020;17(12):757-70.

RTP RESEARCH TO PRACTICE

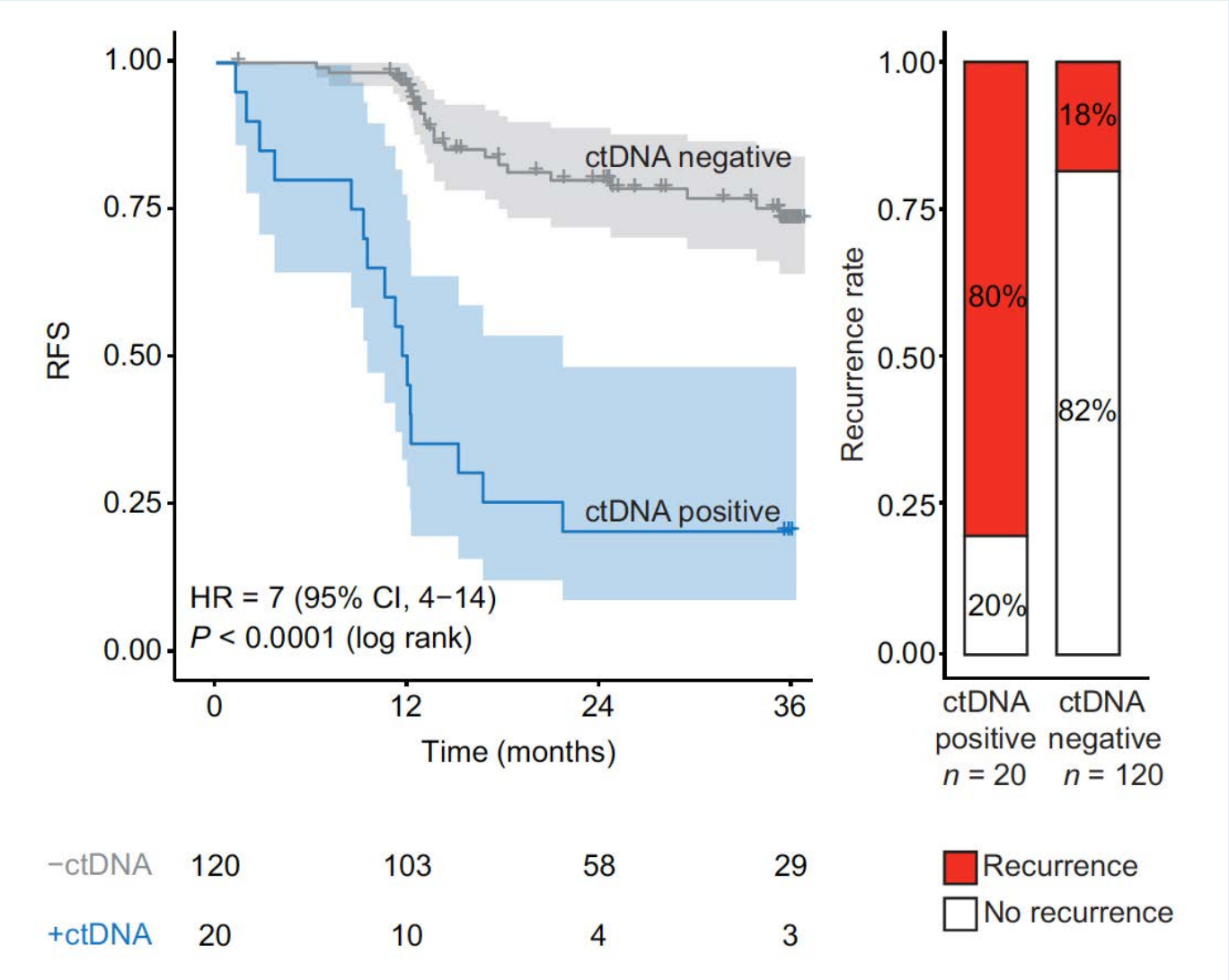
CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Circulating Tumor DNA in Stage III Colorectal Cancer, beyond Minimal Residual Disease Detection, toward Assessment of Adjuvant Therapy Efficacy and Clinical Behavior of Recurrences

Tenna Vesterman Henriksen[1,2], Noelia Tarazona[3,4], Amanda Frydendahl[1,2], Thomas Reinert[1,2], Francisco Gimeno-Valiente[3], Juan Antonio Carbonell-Asins[3,5], Shruti Sharma[6], Derrick Renner[6], Dina Hafez[6], Desamparados Roda[3,4], Marisol Huerta[3], Susana Roselló[3,4], Anders Husted Madsen[7], Uffe S. Løve[8], Per Vadgaard Andersen[9], Ole Thorlacius-Ussing[10], Lene Hjerrild Iversen[11], Kåre Andersson Gotschalck[12], Himanshu Sethi[6], Alexey Aleshin[6], Andres Cervantes[3,4], and Claus Lindbjerg Andersen[1,2]

Clin Cancer Res 2022;28(3):507-17.

Detection of ctDNA After Surgery and Recurrence Rates



Henriksen TV et al. *Clin Cancer Res* 2022;28(3):507-17.

2022 ASCO® ANNUAL MEETING

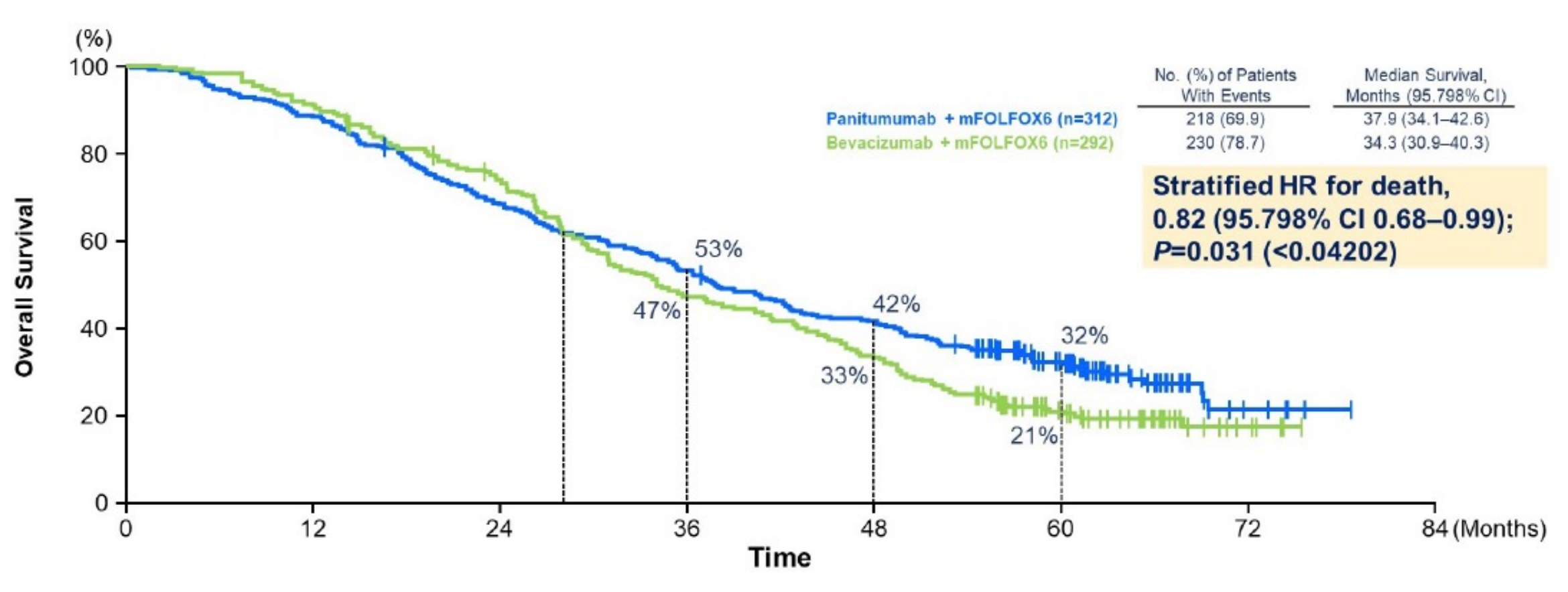
Abstract LBA1

Panitumumab plus mFOLFOX6 versus Bevacizumab plus mFOLFOX6 as first-line treatment in patients with *RAS* wild-type metastatic colorectal cancer: results from the phase 3 PARADIGM trial

Takayuki Yoshino[1], Jun Watanabe[2], Kohei Shitara[1], Kentaro Yamazaki[3], Hisatsugu Ohori[4], Manabu Shiozawa[5], Hirofumi Yasui[4], Eiji Oki[6], Takeo Sato[7], Takeshi Naitoh[8], Yoshito Komatsu[9], Takeshi Kato[10], Masamitsu Hihara[11], Junpei Soeda[11], Kouji Yamamoto[12], Kiwamu Akagi[13], Atsushi Ochiai[14], Hiroyuki Uetake[15], Katsuya Tsuchihara[16], Kei Muro[17]

RTP RESEARCH TO PRACTICE

PARADIGM: Overall Survival for Patients with Left-Sided CRC (Primary Endpoint 1)



Yoshino T et al. ASCO 2022;Abstract LBA1.

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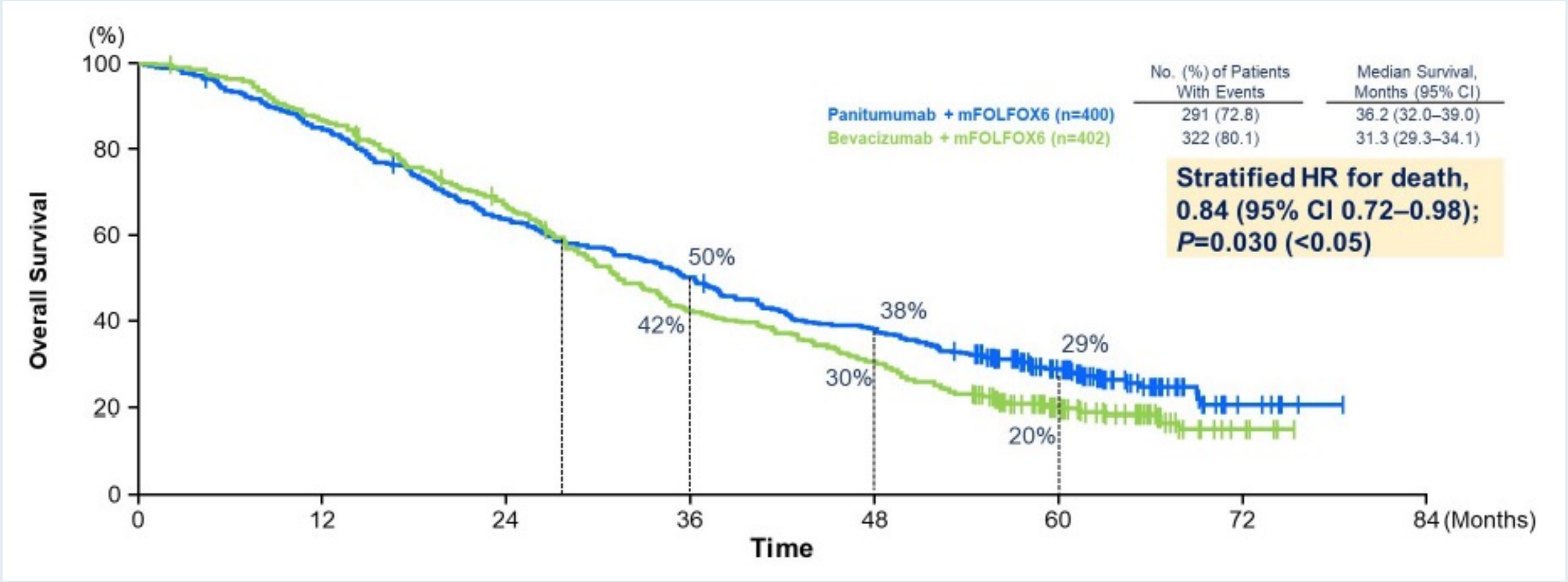
PARADIGM: Overall Survival in the Overall Population (Primary Endpoint 2)



Yoshino T et al. ASCO 2022;Abstract LBA1.

RTP RESEARCH TO PRACTICE

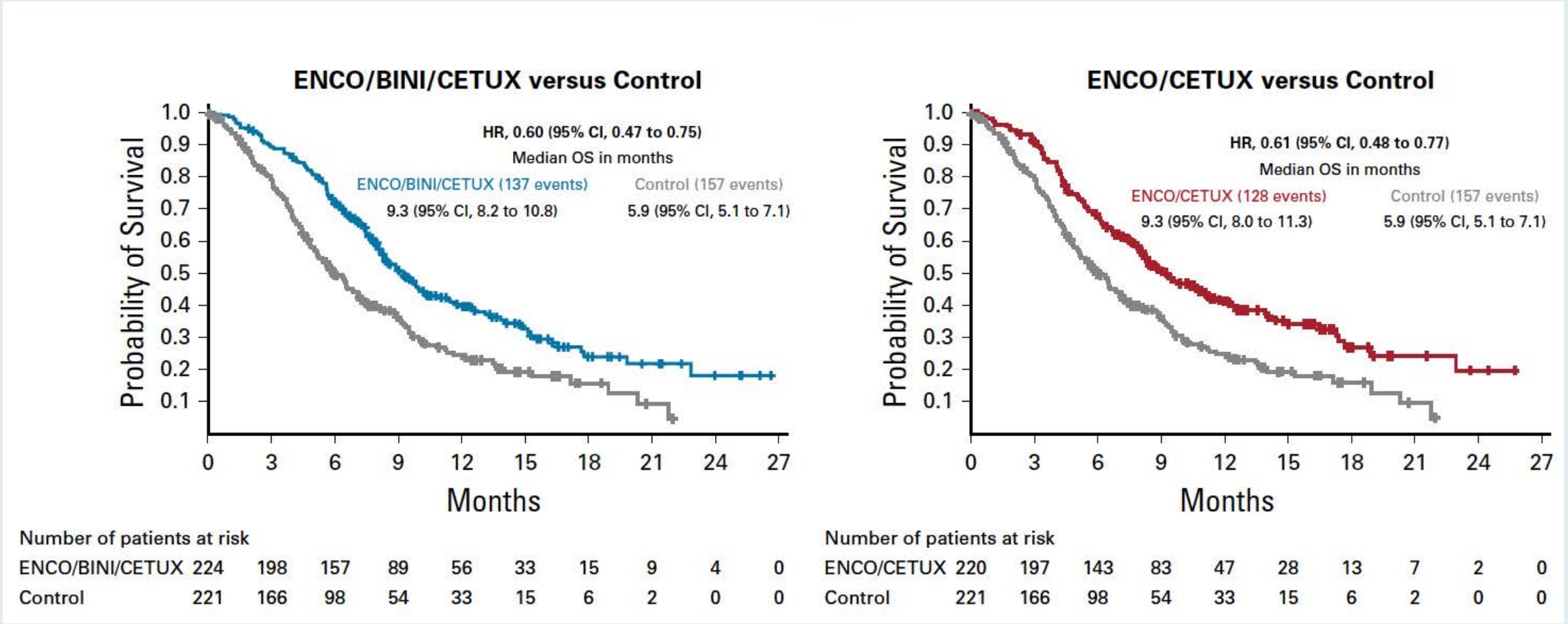
rapid communications

Encorafenib Plus Cetuximab as a New Standard of Care for Previously Treated *BRAF* V600E–Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study

Josep Tabernero, MD, PhD[1]; Axel Grothey, MD[2]; Eric Van Cutsem, MD, PhD[3]; Rona Yaeger, MD[4]; Harpreet Wasan, MD[5]; Takayuki Yoshino, MD, PhD[6]; Jayesh Desai, MBBS[7]; Fortunato Ciardiello, MD, PhD[8]; Fotios Loupakis, MD, PhD[9]; Yong Sang Hong, MD, PhD[10]; Neeltje Steeghs, MD, PhD[11]; Tormod Kyrre Guren, MD, PhD[12]; Hendrik-Tobias Arkenau, MD, PhD[13]; Pilar Garcia-Alfonso, MD[14]; Elena Elez, MD, PhD[1]; Ashwin Gollerkeri, MD[15]; Kati Maharry, PhD[15]; Janna Christy-Bittel, MSN[15]; and Scott Kopetz, MD, PhD[16]

J Clin Oncol 2021;39(4):273-84.

BEACON: Overall Survival Results



Tabanero J et al. *J Clin Oncol* 2021;39(4):273-84.

WORLD CONGRESS ON Gastrointestinal Cancer

ANCHOR CRC: a single-arm, phase 2 study of encorafenib, binimetinib plus cetuximab in previously untreated *BRAF*^{V600E}–mutant metastatic colorectal cancer

Eric Van Cutsem, Julien Taieb, Rona Yaeger, Takayuki Yoshino, Evaristo Maiello, Elena Elez Fernandez, Jeroen Dekervel, Paul Ross, Ana Ruiz Casado, Janet Graham, Takeshi Kato, Jose Carlos Ruffinelli, Thierry André, Edith Carrière Roussel, Isabelle Klauck, Mélanie Groc, Axel Grothey, Jean-Claude Vedovato, Josep Tabernero*

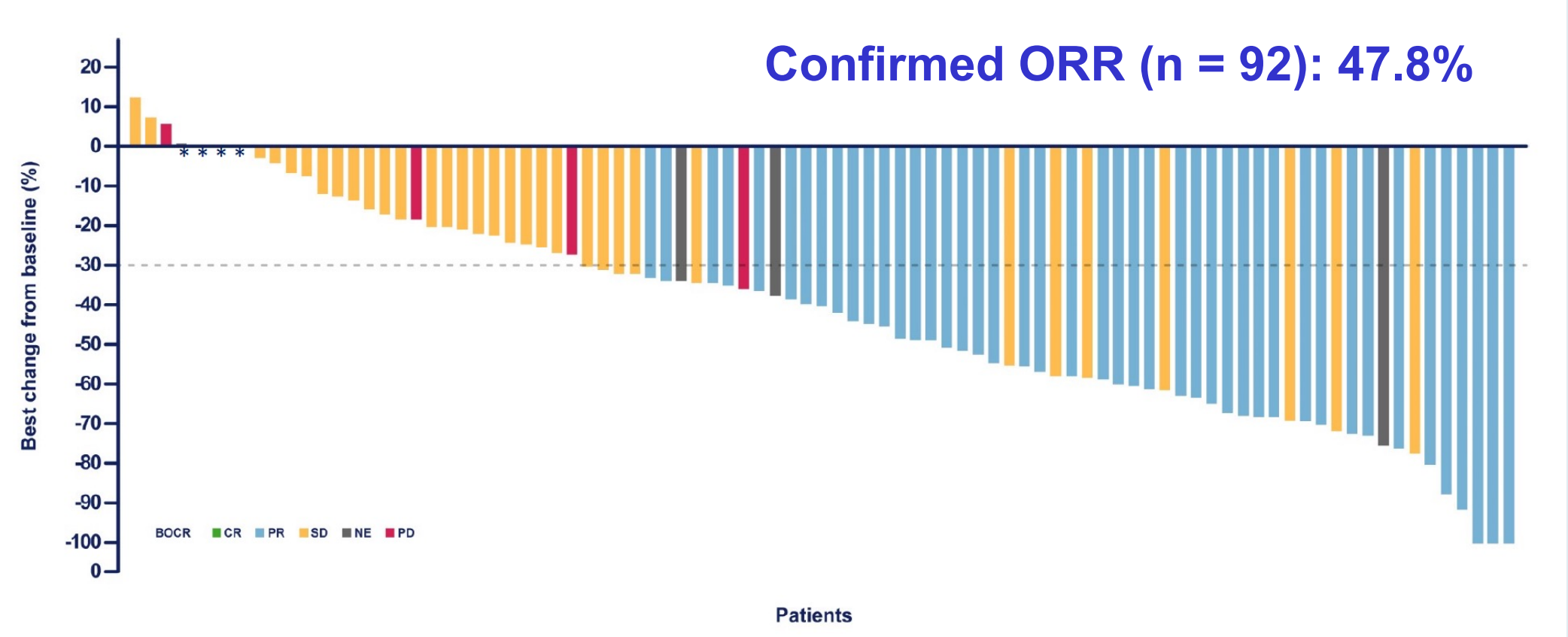
** University Hospitals Leuven, Belgium*

ANCHOR CRC: encorAfenib, biNimetinib and Cetuximab in subjects witH previOusly untreated BRAF-mutant ColoRectal Cancer

ESMO World Congress on Gastrointestinal Cancer 2021;Abstract O-10.

RTP RESEARCH TO PRACTICE

ANCHOR CRC: Results Summary



ORR = objective response rate.

- Overall survival was 17.2 mo (with a median follow-up of 14.4 mo)
- The triplet combination was well tolerated and there were no unexpected toxicities

Van Cutsem E et al. ESMO World Congress on Gastrointestinal Cancer 2021;Abstract O-10.

BREAKWATER Study Design

An open-label, multicenter, randomized phase 3 study of 1st line encorafenib plus cetuximab with or without chemotherapy versus standard of care therapy in patients with metastatic *BRAF* V600E-mutant mCRC

Safety lead-in

Patients with *BRAF*^{V600E} mutant mCRC with 0 to 1 prior regimens in the metastatic setting

Phase 3

Patients with *BRAF*^{V600E} mutant mCRC and no prior systemic therapy in the metastatic setting

Encorafenib + cetuximab + mFOLFOX6
N=30
Encorafenib + cetuximab + FOLFIRI
N=30

Dosages
- Encorafenib, 300 mg PO QD
- Cetuximab, 500 mg/m² IV Q2W
- **FOLFOX, full dose IV Q2W**
- FOLFIRI, full dose IV Q2W

Randomize 1:1:1*

Arm A**
Encorafenib + cetuximab, N=290

Arm B**
Encorafenib + cetuximab + FOLFOX or FOLFIRI$^{\beta}$, N=290

Control arm§
Physician's choice: FOLFOX, FOLFIRI, FOLFOXIRI, CAPOX, all ± anti-VEGF antibody, N=290

PRIMARY ENDPOINTS
PFS (BICR) Arm A vs Control
AND
PFS (BICR) Arm B vs Control
(BICR, blinded independent central review)

KEY SECONDARY ENDPOINTS
OS Arm A vs Control
AND
OS Arm B vs Control

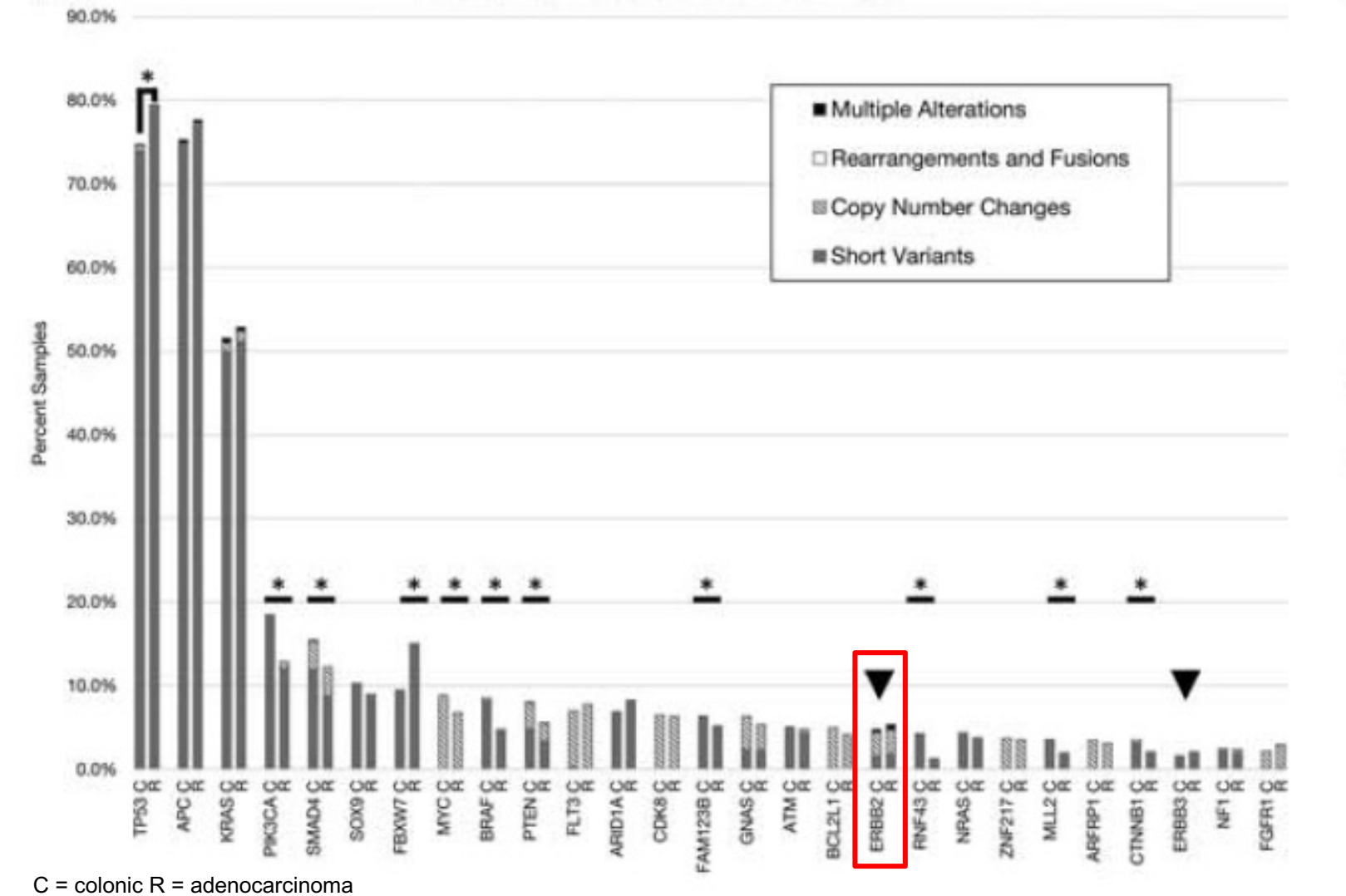
OTHER ENDPOINTS
- Incidence of DLTs, adverse events, dose modifications/discontinuations due to AEs
- PK including drug-drug interactions

BREAKWATER STUDY

*Stratified by: ECOG PS 0 v. 1, Region US/Canada v. Western Europe v. ROW
**Same dosing as SLI; $^{\beta}$FOLFOX or FOLFIRI based on SLI results; § No crossover.
ClinicalTrials.gov Identifier: NCT04607421

Van Cutsem E et al. ESMO World Congress on Gastrointestinal Cancer 2021;Abstract O-10.

HER2 (ERBB2) Mutation Frequency in 8,887 Consecutive Cases of Metastatic CRC (mCRC)



C = colonic R = adenocarcinoma

A total of 569 samples (6.4%) harbored alterations affecting ERBB2

Of the mCRC cases with ERBB2 alterations,

- 251 (58.1%) featured samples with ERBB2 amplification only
- 135 (31.5%) featured a short-variant sequence alteration in ERBB2
- 35 (8.2%) featured co-occurring short-variant and amplification alterations in ERBB2

Ross JS et al. *Cancer* 2018; 124(7):1358-73.

Results from the Pivotal MOUNTAINEER Trial Demonstrate Clinically Meaningful Antitumor Activity of Tucatinib with Trastuzumab for Previously Treated HER2-Positive mCRC

Press Release – July 2, 2022

"…Today announced full results from the pivotal phase 2 MOUNTAINEER trial, which showed tucatinib in combination with trastuzumab was well-tolerated with durable responses in patients with previously treated HER2-positive metastatic colorectal cancer (mCRC).

At a median duration of follow-up of 20.7 months (interquartile range: 11.7, 39.0), results of the MOUNTAINEER trial showed a 38.1% confirmed objective response rate (cORR) (95% Confidence Interval [CI]: 27.7, 49.3) per blinded independent central review (BICR) in the HER2-positive patients who were assigned to receive tucatinib in combination with trastuzumab (n = 84 with a median age of 55.0 years [range 24 to 77]). In these patients, the median duration of response (DoR) per BICR was 12.4 months (95% CI: 8.5, 20.5). Median progression-free survival per BICR was 8.2 months (95% CI: 4.2, 10.3), and median overall survival was 24.1 months (95% CI: 20.3, 36.7)."

https://finance.yahoo.com/news/seagen-announces-results-pivotal-mountaineer-103500806.html

RTP RESEARCH TO PRACTICE

PARIS 2022 ESMO congress 2022

Additional analyses of MOUNTAINEER: A phase 2 study of tucatinib and trastuzumab for HER2-positive mCRC

John H. Strickler, MD
Duke University Medical Center, Durham, NC, USA

Andrea Cercek, Salvatore Siena, Thierry Andre, Kimmie Ng, Eric Van Cutsem, Christina Wu, Andrew Scott Paulson, Joleen M. Hubbard, Andrew L. Coveler, Christos Fountzilas, Adel Kardosh, Pashtoon Murtaza Kasi, Heinz-Josef Lenz, Kristen Ciombor, Elena Elez, David L. Bajor, Michael Stecher, Wentao Feng, Tanios S. Bekaii-Saab

Abstract LBA27

RTP RESEARCH TO PRACTICE

MOUNTAINEER: Response Analyses

Responses		Tucatinib + Trastuzumab Cohorts A+B n=84[1]	Tucatinib Monotherapy Cohort C n=30	Tucatinib + Trastuzumab Post-Crossover n=28
Best overall response per BICR[a], n (%)	CR	3 (3.6)	0	0
	PR	29 (34.5)	1 (3.3)	5 (17.9)
	SD[b]	28 (33.3)	23 (76.7)	18 (64.3)
	PD	22 (26.2)	4 (13.3)	5 (17.9)
	Not available[c]	2 (2.4)	2 (6.7)	0
ORR per BICR, % (95% CI)[d]		**38.1 (27.7-49.3)[f]**	**3.3 (0.1-17.2)[g]**	**17.9 (6.1-36.9)[f]**
DCR[e] per BICR, n (%)		**60 (71.4)**	**24 (80.0)**	**23 (82.1)**

BICR = blinded independent central review; ORR = objective response rate; DCR = disease control rate

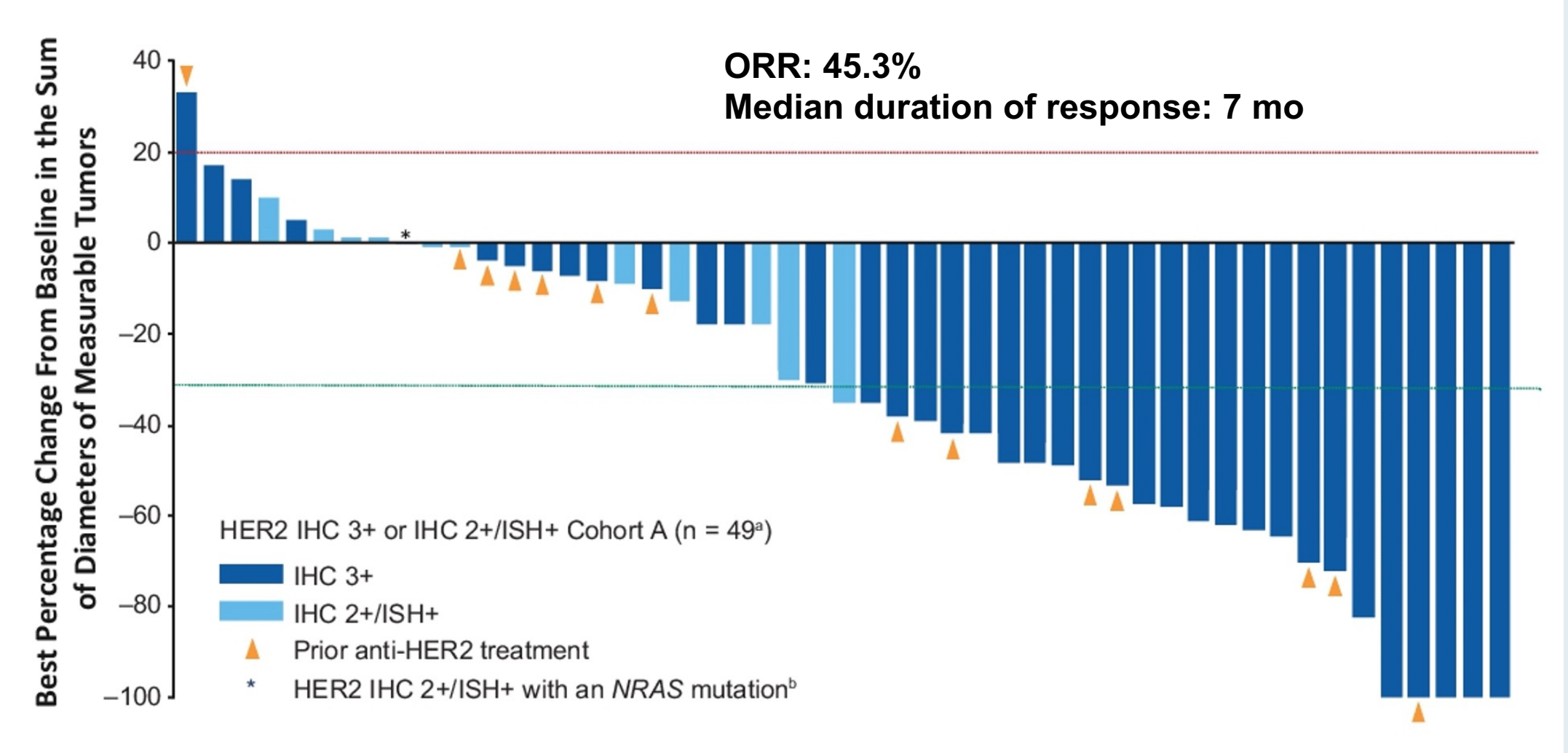
Strickler JH et al. ESMO 2022;Abstract LBA27.

Gastrointestinal Cancers Symposium 2022;Abstract 119.

Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2-expressing Metastatic Colorectal Cancer (mCRC): Final Results From a Phase 2, Multicenter, Open-label Study (DESTINY-CRC01)

Takayuki Yoshino,[1] Maria Di Bartolomeo,[2] Kanwal Raghav,[3] Toshiki Masuishi,[4] Hisato Kawakami,[5] Kensei Yamaguchi,[6] Tomohiro Nishina,[7] Zev Wainberg,[8] Elena Elez,[9] Javier Rodriguez,[10] Marwan Fakih,[11] Fortunato Ciardiello,[12] Kapil Saxena,[13] Kojiro Kobayashi,[13] Emarjola Bako,[13] Yasuyuki Okuda,[14] Gerold Meinhardt,[13] Axel Grothey,[15] Salvatore Siena[16,17]

DESTINY-CRC01 Primary Endpoint: Objective Response Rate (ORR) in Cohort A (IHC 3+ or IHC 2+/ISH+, N = 53)



Yoshino T et al. Gastrointestinal Cancers Symposium 2022;Abstract 119.

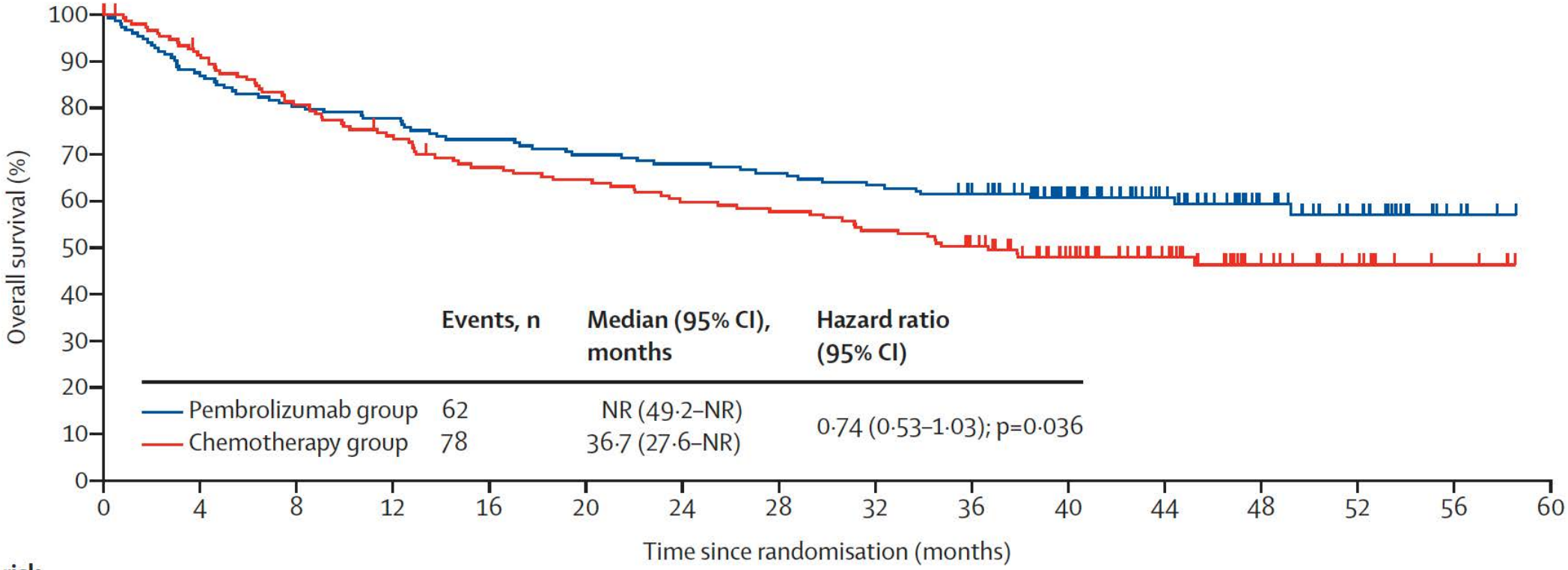
RTP RESEARCH TO PRACTICE

Lancet Oncol 2022 April 12;23:659-70.

Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study

*Luis A Diaz Jr, Kai-Keen Shiu, Tae-Won Kim, Benny Vittrup Jensen, Lars Henrik Jensen, Cornelis Punt, Denis Smith, Rocio Garcia-Carbonero, Manuel Benavides, Peter Gibbs, Christelle de la Fourchardiere, Fernando Rivera, Elena Elez, Dung T Le, Takayuki Yoshino, Wen Yan Zhong, David Fogelman, Patricia Marinello, Thierry Andre, on behalf of the KEYNOTE-177 Investigators**

KEYNOTE-177 Coprimary Endpoint: Overall Survival (ITT)

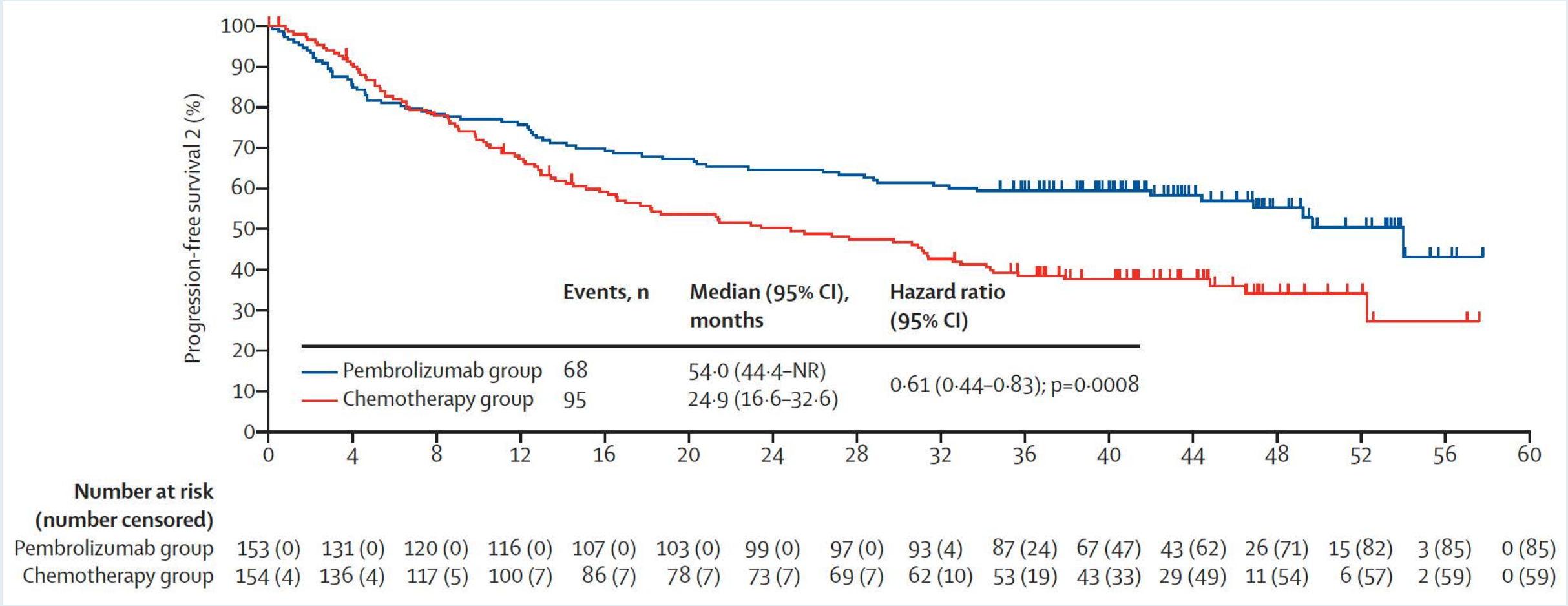


Number at risk (number censored)															
Pembrolizumab group	153 (0)	134 (0)	123 (0)	119 (0)	112 (0)	107 (0)	104 (0)	101 (0)	97 (2)	92 (23)	70 (45)	48 (64)	28 (75)	16 (78)	4 (91)	0 (91)
Chemotherapy group	154 (4)	137 (4)	121 (5)	110 (6)	99 (6)	95 (6)	88 (6)	85 (6)	79 (9)	71 (24)	53 (41)	36 (58)	18 (65)	11 (73)	3 (76)	0 (76)

NR = not reached

Diaz LA Jr et al. *Lancet Oncol* 2022 April 12;23:659-70.

KEYNOTE-177 Coprimary Endpoint: Progression-Free Survival (ITT)



Diaz LA Jr et al. *Lancet Oncol* 2022 April 12;23:659-70.

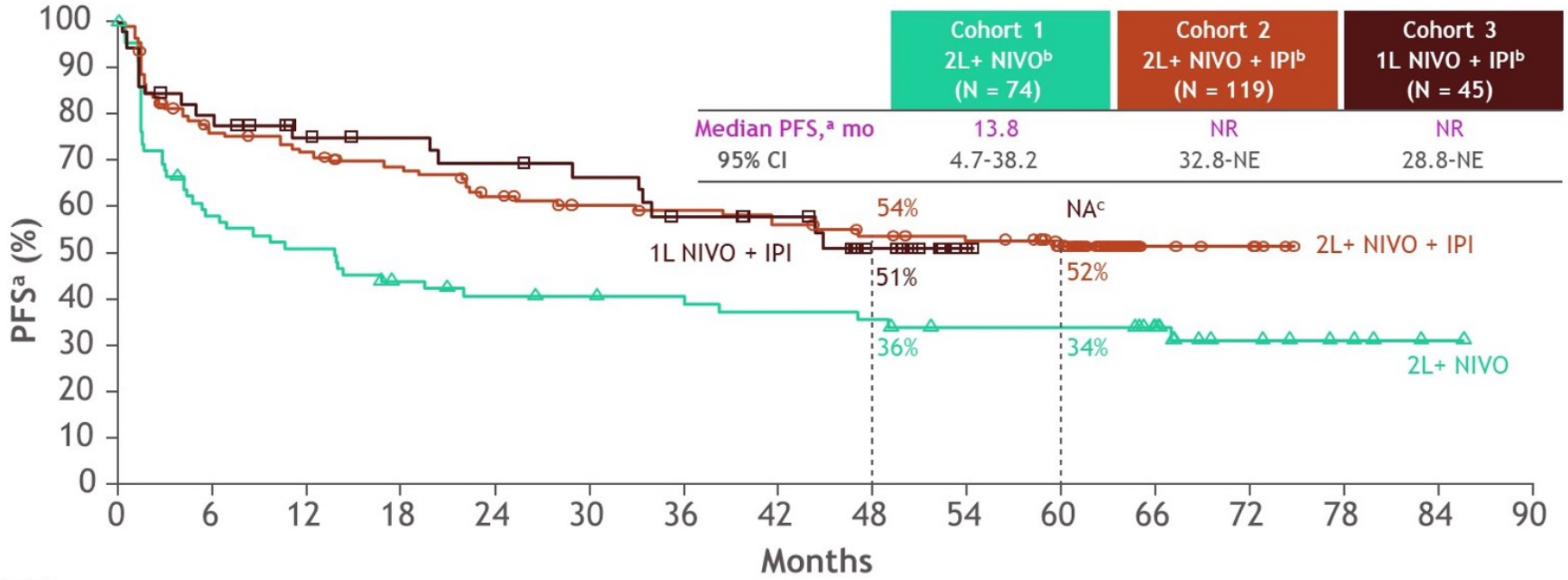
ASCO 2022 | Abstract 3510

Nivolumab ± ipilimumab in patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: ~ 5-year follow-up from CheckMate 142

Michael J. Overman,[1] Heinz-Josef Lenz,[2] Thierry Andre,[3] Massimo Aglietta,[4] Mark Wong,[5] Gabriele Luppi,[6] Eric Van Cutsem,[7] Ray McDermott,[8] Alain Hendlisz,[9] Dana Cardin,[10] Michael Morse,[11] Bart Neyns,[12] Andrew Hill,[13] Maria Luisa Limon,[14] Pilar Garcia-Alfonso,[15] Anuradha Krishnamurthy,[16] Franklin Chen,[17] Sandzhar Abdullaev,[18] Samira Soleymani,[18] Sara Lonardi[19]

[1]University of Texas MD Anderson Cancer Center, Houston, TX; [2]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; [3]Hôpital Saint Antoine, Assistance Publique Hôpitaux de Paris and Sorbonne Université, Paris, France; [4]Candiolo Cancer Institute and University of Torino Medical School, Candiolo, Italy; [5]Westmead Hospital, Sydney, Australia; [6]University Hospital of Modena, Modena, Italy; [7]University Hospitals Gasthuisberg/Leuven and KU Leuven, Leuven, Belgium; [8]St Vincent's University Hospital and Cancer Trials Ireland, Dublin, Ireland; [9]Institut Jules Bordet, Brussels, Belgium; [10]Vanderbilt-Ingram Cancer Center, Nashville, TN; [11]Duke University Medical Center, Durham, NC; [12]Universitair Ziekenhuis Brussel, Brussels, Belgium; [13]Tasman Oncology Research Ltd, Southport, Australia; [14]Hospital Universitario Virgen del Rocio, Sevilla, Spain; [15]Hospital Gral Universitario Gregorio Marañon, Madrid, Spain; [16]University of Pittsburgh Cancer Institute, Pittsburgh, PA; [17]Novant Health Cancer Institute, Winston-Salem, NC; [18]Bristol Myers Squibb, Princeton, NJ; [19]Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

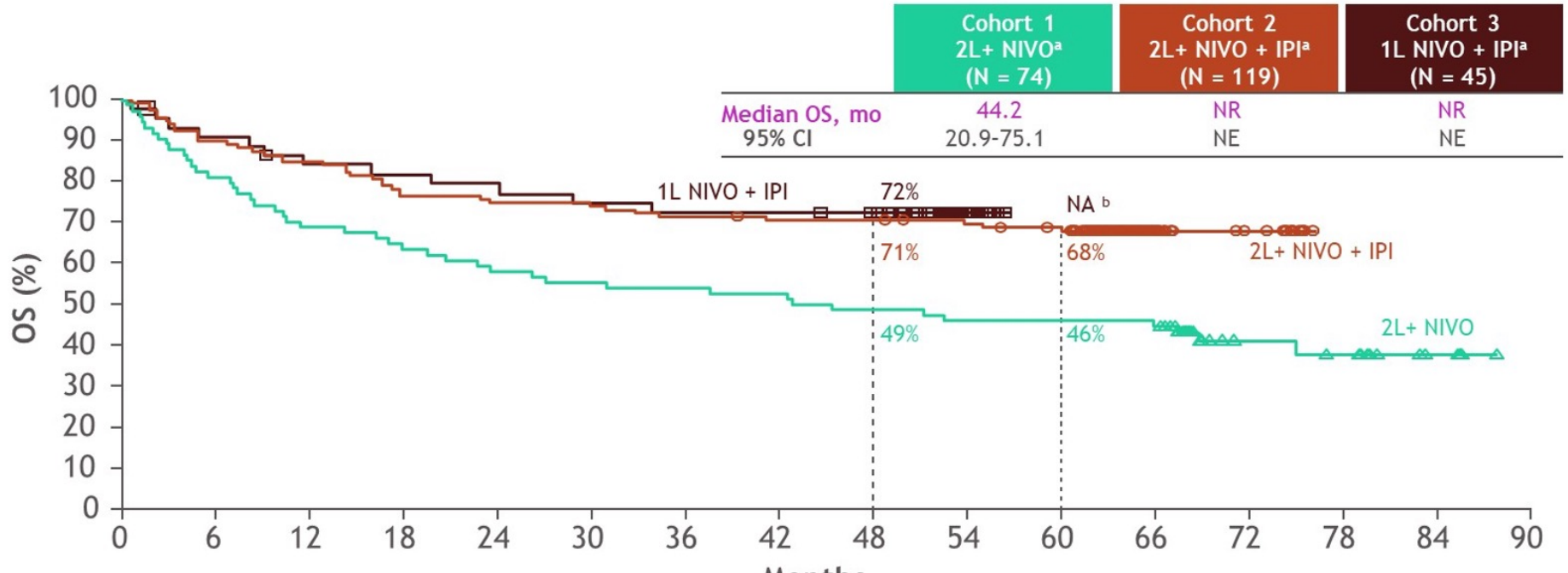
CheckMate 142: Progression-Free Survival (PFS)



- Median PFS was 13.8 months in cohort 1 and not reached in cohorts 2 and 3
  - 48-month PFS rates were 36% (cohort 1), 54% (cohort 2), and 51% (cohort 3)
  - 60-month PFS rates were 34% (cohort 1), 52% (cohort 2), and not available for cohort 3

Overman MJ et al. ASCO 2022;Abstract 3510.

CheckMate 142: Overall Survival (OS)



- Median OS was 44.2 months in cohort 1 and not reached in cohorts 2 and 3
  - 48-month OS rates were 49% (cohort 1), 71% (cohort 2), and 72% (cohort 3)
  - 60-month OS rates were 46% (cohort 1), 68% (cohort 2), and not available for cohort 3

Overman MJ et al. ASCO 2022;Abstract 3510.

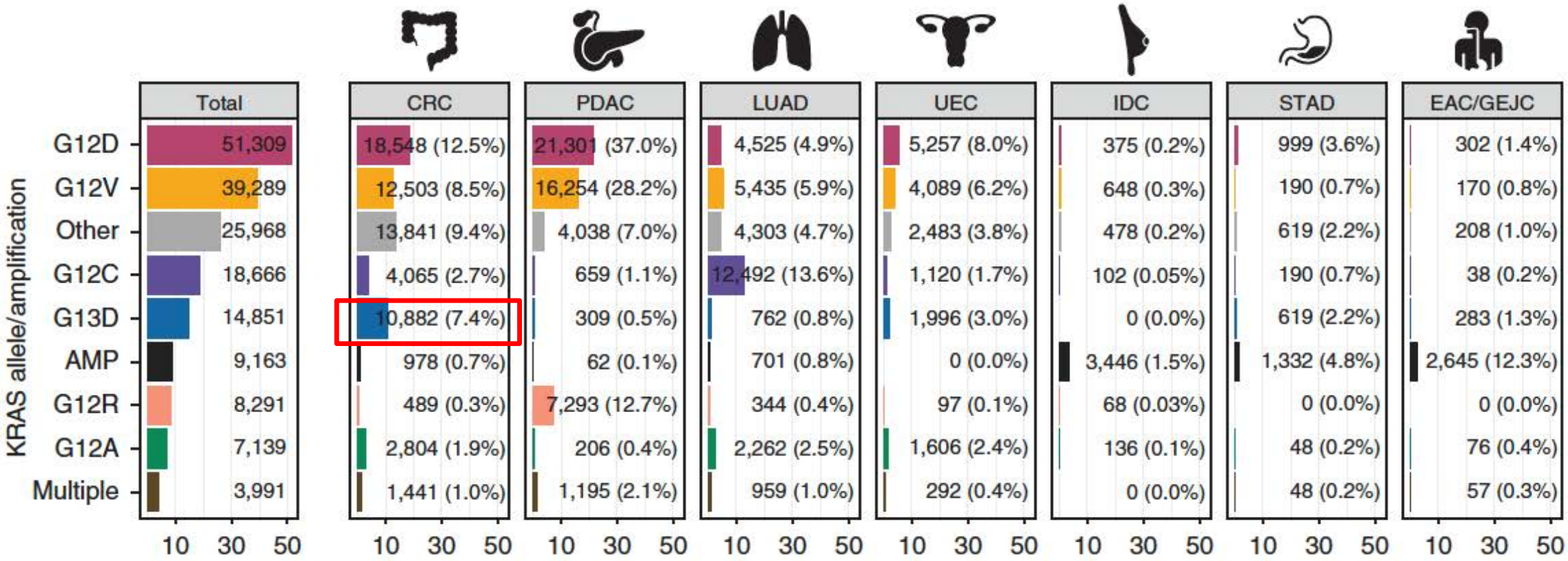
CheckMate 142: Response, Disease Control and Durability by Cohort

Outcome[a]	Cohort 1 2L+ NIVO[b] (N = 74)	Cohort 2 2L+ NIVO + IPI[b] (N = 119)	Cohort 3 1L NIVO + IPI[b] (N = 45)
ORR,[c] n (%)	29 (39)	77 (65)	32 (71)
95% CI	28-51	55-73	56-84
Best overall response, n (%)			
CR	12 (16)	20 (17)	9 (20)
PR	17 (23)	57 (48)	23 (51)
SD	22 (30)	25 (21)	6 (13)
PD	19 (26)	14 (12)	7 (16)
Unable to determine	4 (5)	3 (3)	0
DCR,[d] n (%)	51 (69)	96 (81)	38 (84)
95% CI	57-79	72-87	71-94
Median TTR (range),[e] months	2.8 (1.2-46.3)	2.8 (1.1-37.1)	2.7 (1.2-27.7)
Median DOR (95% CI),[e] months	NR (NE)	NR (NE)	NR (41.5-NE)
36-month rate (95% CI), %	81 (60-92)	79 (67-87)	75 (52-88)
42-month rate (95% CI), %	77 (55-89)	75 (63-84)	69 (44-84)
60-month rate (95% CI), %	77 (55-89)	73 (60-82)	NA

ORR = objective response rate; DCR = disease control rate; TTR = time to response; DOR = duration of response

Overman MJ et al. ASCO 2022;Abstract 3510.

KRAS Mutations: Estimated New Diagnoses or Patients per Year in the United States



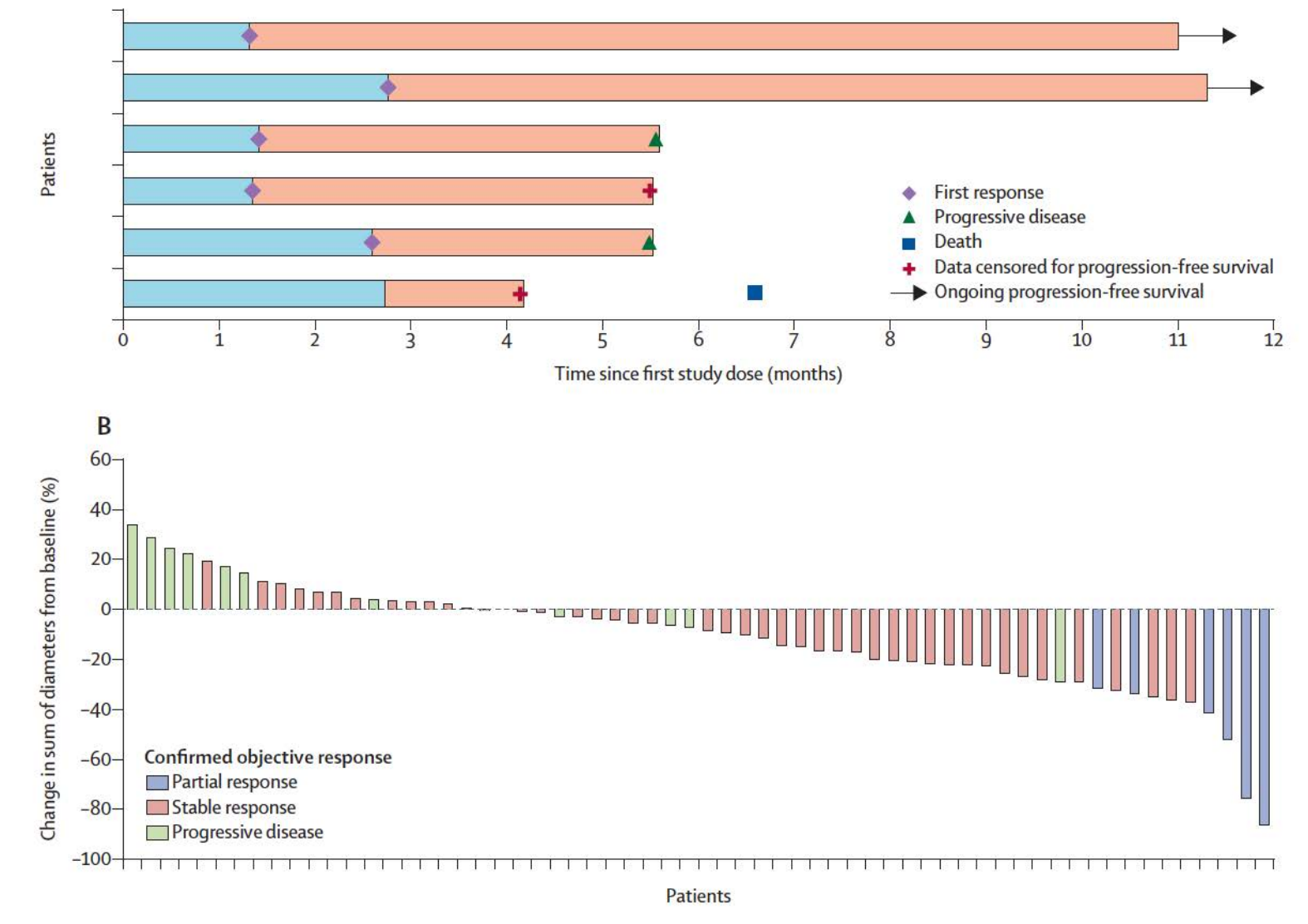
Hofmann MH et al. *Cancer Discov* 2022 April 1;12(4):924-37.

Lancet Oncol 2022;23(1):115-24.

Sotorasib for previously treated colorectal cancers with *KRAS*^{G12C} mutation (CodeBreaK100): a prespecified analysis of a single-arm, phase 2 trial

Marwan G Fakih, Scott Kopetz*, Yasutoshi Kuboki, Tae Won Kim, Pamela N Munster, John C Krauss, Gerald S Falchook, Sae-Won Han, Volker Heinemann, Kei Muro, John H Strickler, David S Hong, Crystal S Denlinger, Gustavo Girotto, Myung-Ah Lee, Haby Henary, Qui Tran, Joseph K Park, Gataree Ngarmchamnanrith, Hans Prenen, Timothy J Price*

CodeBreaK 100: Efficacy of Sotorasib



Fakih MG et al. *Lancet Oncol* 2022;23(1):115-24.

PARIS 2022 ESMO congress

KRYSTAL-1: Updated Efficacy and Safety of Adagrasib (MRTX849) With or Without Cetuximab in Patients With Advanced Colorectal Cancer (CRC) Harboring a KRAS^{G12C} Mutation

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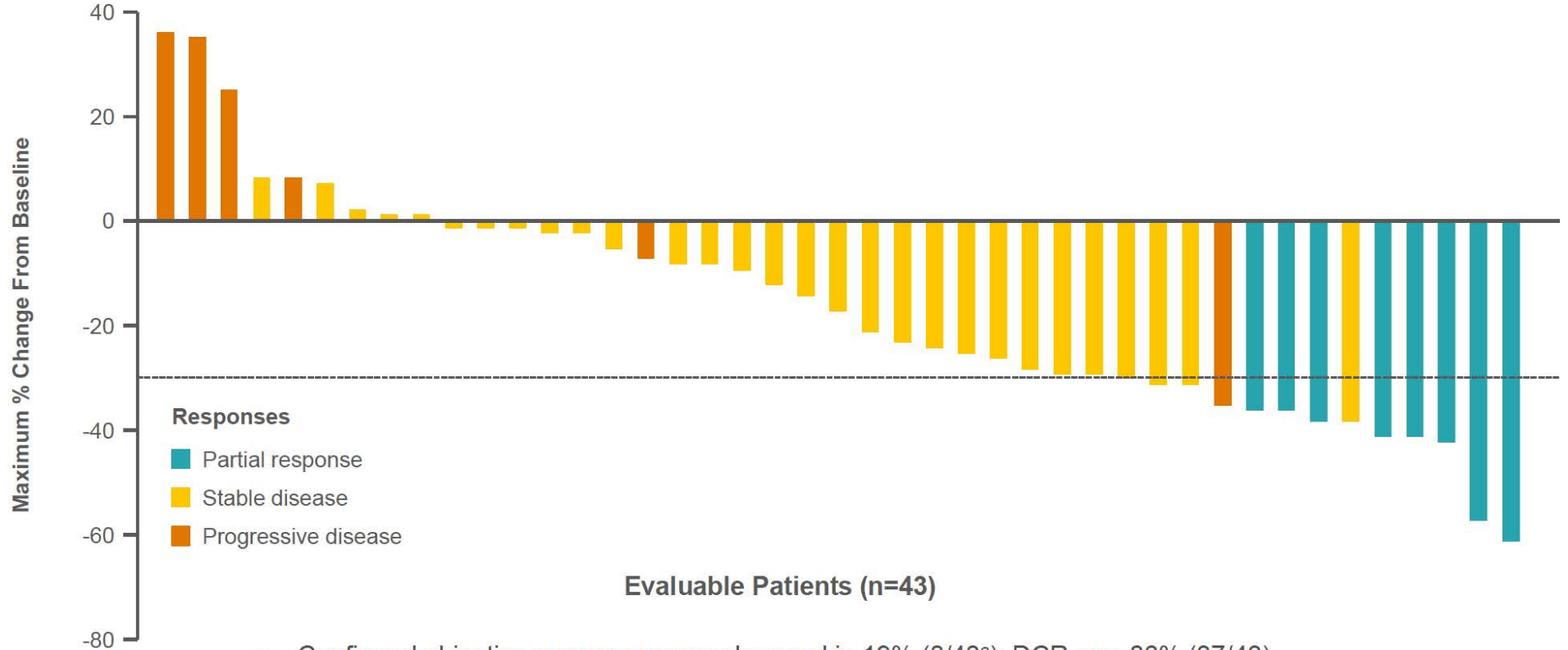
Abstract LBA24

RTP RESEARCH TO PRACTICE

Adagrasib Monotherapy in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: Best Tumor Change From Baseline

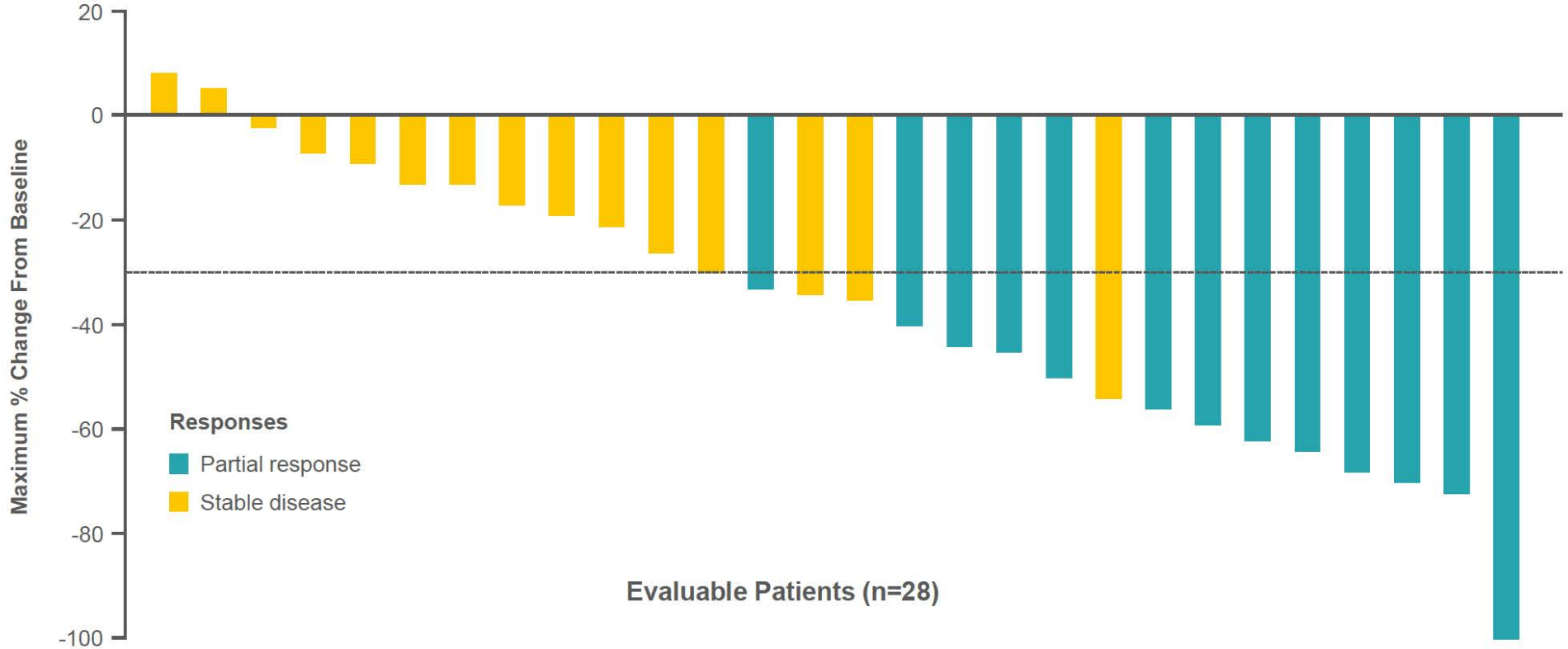


- Confirmed objective responses were observed in 19% (8/43[a]); DCR was 86% (37/43)
- Tumor shrinkage of any magnitude occurred in 79% of patients

[a]Response per investigator assessment (n=43; one patient withdrew consent prior to the first scan)
Data as of June 16, 2022 (median follow-up, 20.1 months)

Klemper SJ et al. ESMO 2022;Abstract LBA24.

Adagrasib + Cetuximab in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: Best Tumor Change From Baseline



- Confirmed objective responses were observed in 46% (13/28[a]); DCR was 100% (28/28)
- Tumor shrinkage of any magnitude occurred in 93% of patients

[a]Response per investigator assessment (n=28; four patients are not included due to no post-baseline assessment of target lesions)
Data as of June 16, 2022 (median follow-up, 17.5 months)

Klemper SJ et al. ESMO 2022;Abstract LBA24.

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Recent Studies in Gastroesophageal and Gastric Cancer

Wells Messersmith, MD
Professor and Head, Medical Oncology
Chief Medical Officer, Oncology Services

Example Case

- 62-year-old patient presents with dysphagia. EGD reveals a **GEJ mass** – biopsy reveals moderately-differentiated adenocarcinoma, pMMR, Her2 IHC negative, CPS=1.
- CT c/a/p reveals cT3N1M0 disease, without evidence of metastases.
- No other medical problems, patient is healthy and works full time.
- ECOG performance status = 0
- What is your initial recommendation for therapy?
  - Surgery
  - Chemoradiation followed by surgery
  - Induction chemotherapy followed by surgery
  - Definitive chemoradiation

CROSS Trial - Neoadjuvant chemoRT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, D.J. Richel, G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta, R.J.B. Blaisse, O.R.C. Busch, F.J.W. ten Kate, G.-J. Creemers, C.J.A. Punt, J.T.M. Plukker, H.M.W. Verheul, E.J. Spillenaar Bilgen, H. van Dekken, M.J.C. van der Sangen, T. Rozema, K. Biermann, J.C. Beukema, A.H.M. Piet, C.M. van Rij, J.G. Reinders, H.W. Tilanus, and A. van der Gaast, for the CROSS Group*

- Paclitaxel 50 mg/m2 + Carboplatin AUC=2 on Days 1, 8, 15, 22 and 29
- Concurrent radiation of 41.4Gy in 23 fractions of 1.8 Gy
- Surgery within 6 weeks of completion of chemoRT

Van Hagen, NEJM 2012

CROSS Trial

- T3N0-1 75%
- Median Age 60
- 74% Adenocarcinoma
- 93% received all courses of chemotherapy
- 23% had ≥ Grade 3 toxicity from pre-op therapy

Resection rate of all randomized patients

	Surgery alone	CRT + surgery	
	186/188 (99%)	168/178 (95%)	

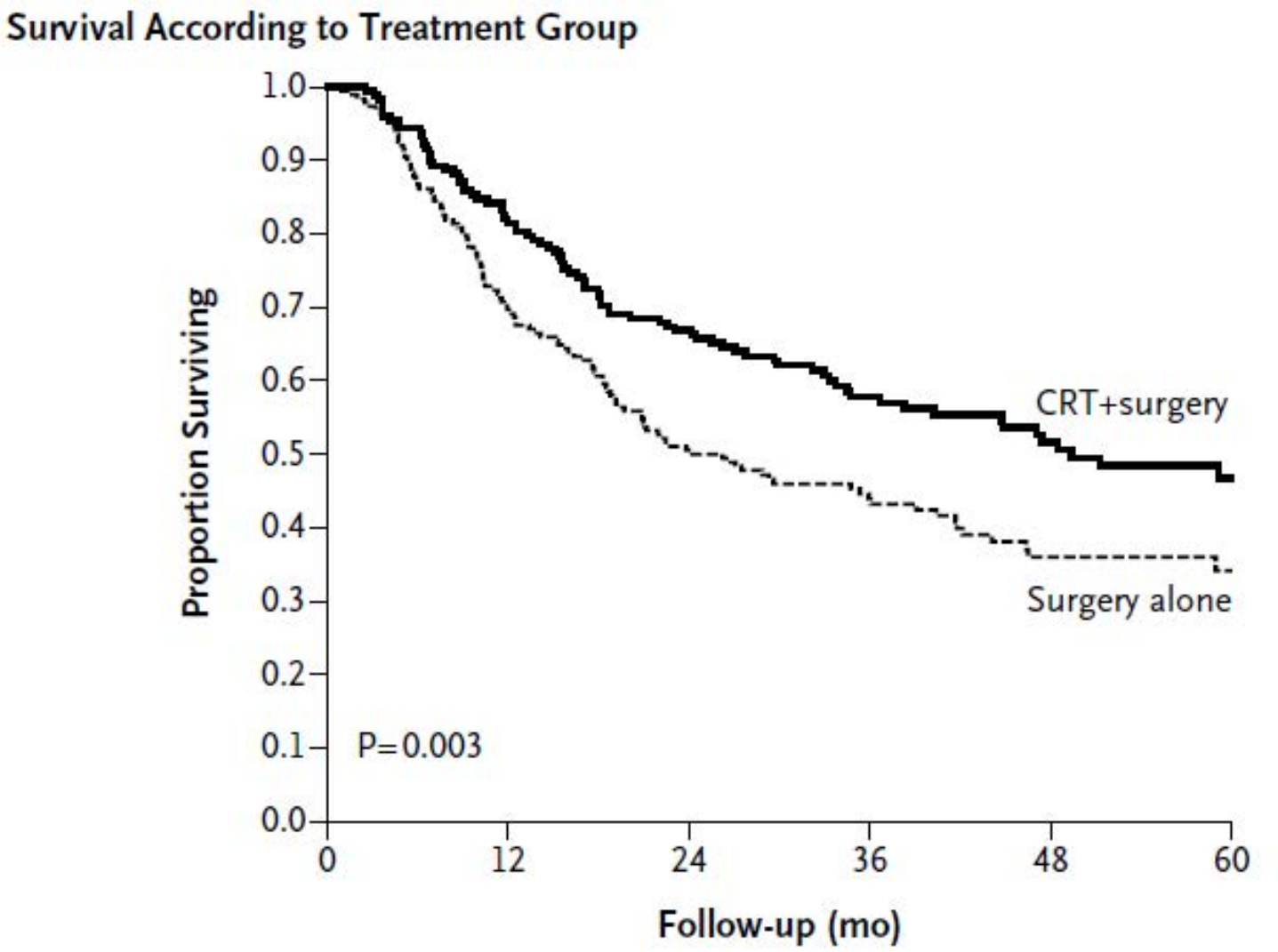
Resection margins

	Surgery alone	CRT + surgery	
R0	111/161 (69%)	148/161 (92%)	p<0.002

R0 = no tumor within 1 mm of the resection margins

Van Hagen, NEJM 2012

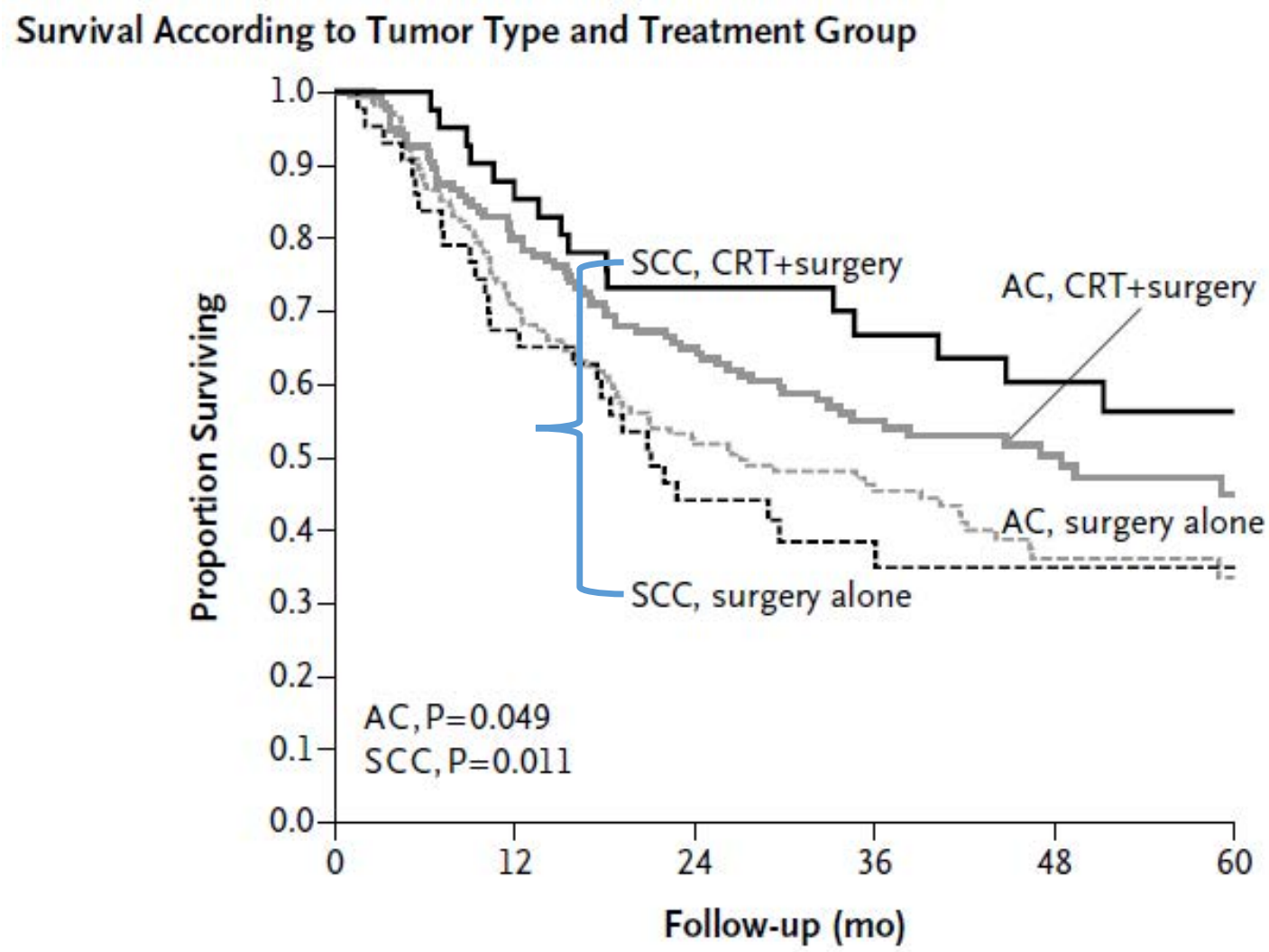
CROSS Trial - Neoadjuvant chemoRT



- 5 yr survival: 47% v 34%
- Median survival 49 v 24 months HR 0.66, p=0.003
- Squamous HR 0.453, Adeno HR 0.732
- Squamous pCR 49%, Adeno 23% (p=0.008)

Van Hagen, NEJM 2012

CROSS Trial: OS according to tumor type and treatment group



- Especially impactful for the SCC group

Van Hagen, NEJM 2012

CROSS Trial

Table 2. Adverse Events during Neoadjuvant Chemoradiotherapy and after Surgery.*

Event	Chemoradiotherapy and Surgery (N=171)	Surgery Alone (N=186)
Postoperative events — no. of patients/total no. (%)†		
Pulmonary complications‡	78/168 (46)	82/186 (44)
Cardiac complications§	36/168 (21)	31/186 (17)
Chylothorax¶	17/168 (10)	11/186 (6)
Mediastinitis‖	5/168 (3)	12/186 (6)
Anastomotic leakage**	36/161 (22)	48/161 (30)
Death		
In hospital	6/168 (4)	8/186 (4)
After 30 days	4/168 (2)	5/186 (3)

Van Hagen, NEJM 2012

Example Case (2)

- The patient underwent chemoradiation with carboplatin/taxol, which he tolerated fairly well.
- He then underwent surgery.
- Pathology showed ypT2N0, with evidence of moderate treatment effect.
- He has recovered uneventfully.
- What do you recommend next?
  - Adjuvant chemotherapy with carbo/taxol
  - Adjuvant chemotherapy with FOLFOX
  - Adjuvant nivolumab
  - Surveillance only

Role of Adjuvant Nivolumab after CROSS regimen

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*

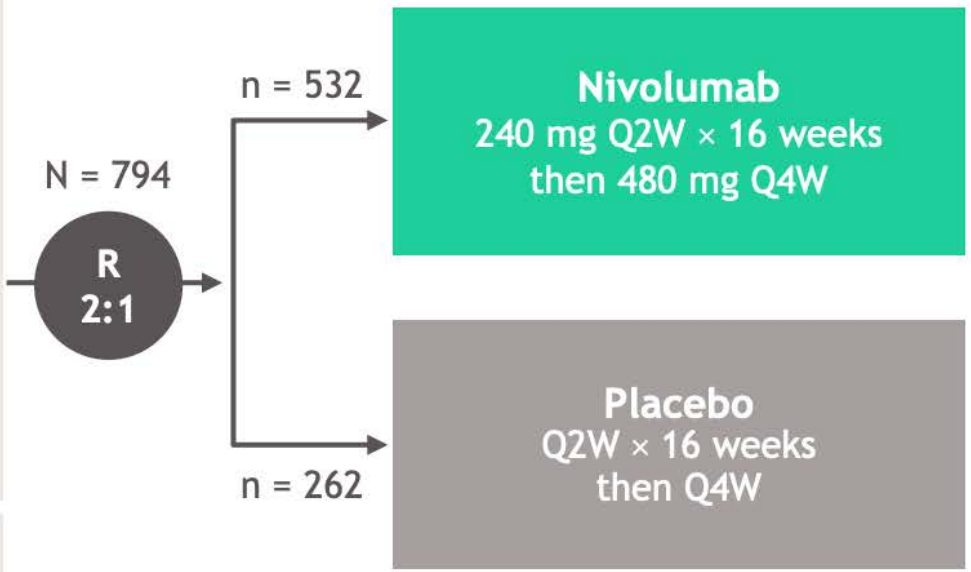
Checkmate-577 Design

Key eligibility criteria

- Stage II/III EC/GEJC
- 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).

Kelly, NEJM 2021

Checkmate-577 baseline characteristics

Baseline characteristics

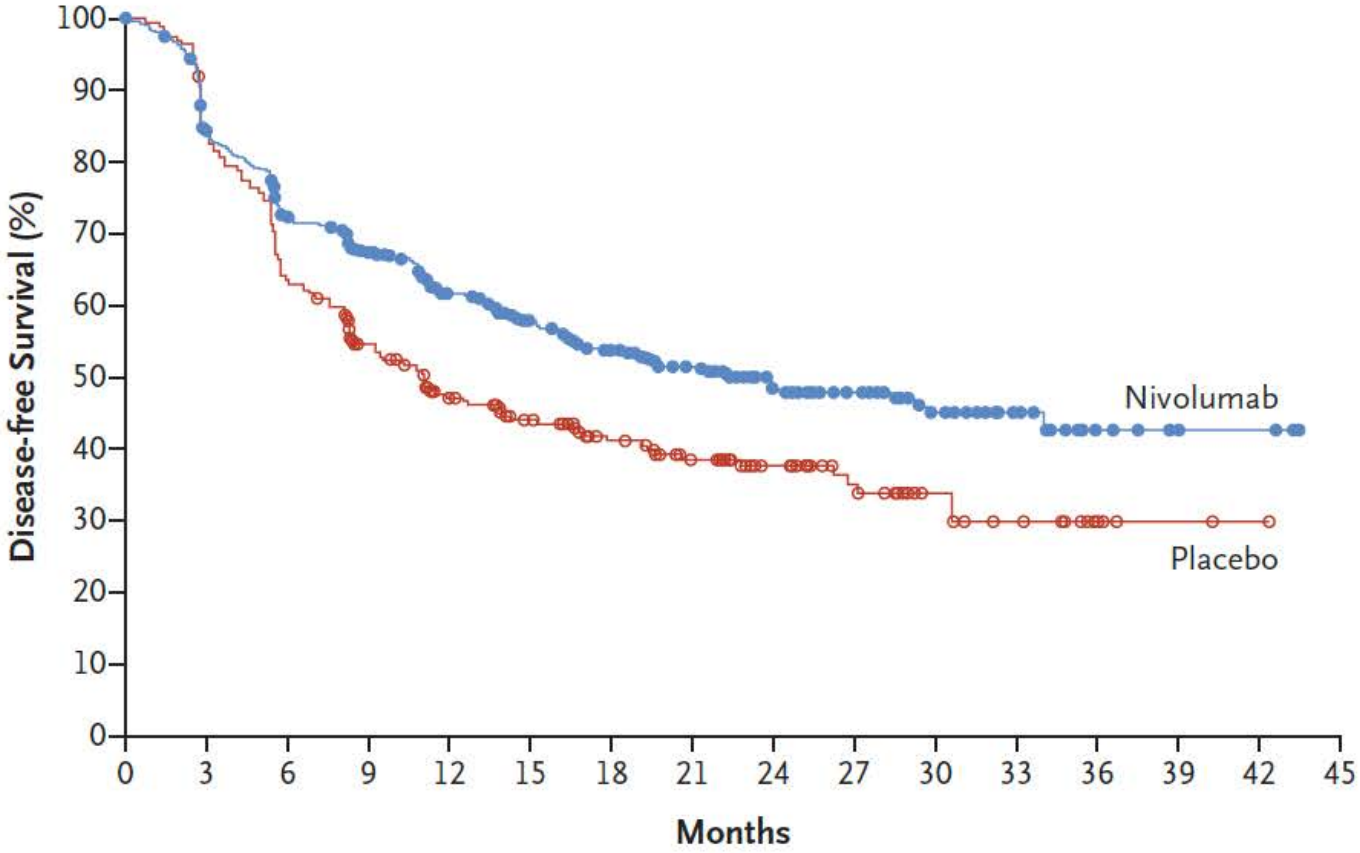
	Nivolumab (n = 532)	Placebo (n = 262)
Median age (range), years	62.0 (26-82)	61.0 (26-86)
Male, %	84	85
Race,[a] %		
White	81	82
Asian	16	13
ECOG PS, %		
0	58	60
1	42	40
Disease stage at initial diagnosis, %		
II	34	38
III	66	62
Tumor location, %		
EC	60	59
GEJC	40	41
Histology, %		
Squamous cell carcinoma	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).

Kelly, NEJM 2021

Checkmate-577: Disease-Free Survival

A Disease-free Survival in the Overall Population



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

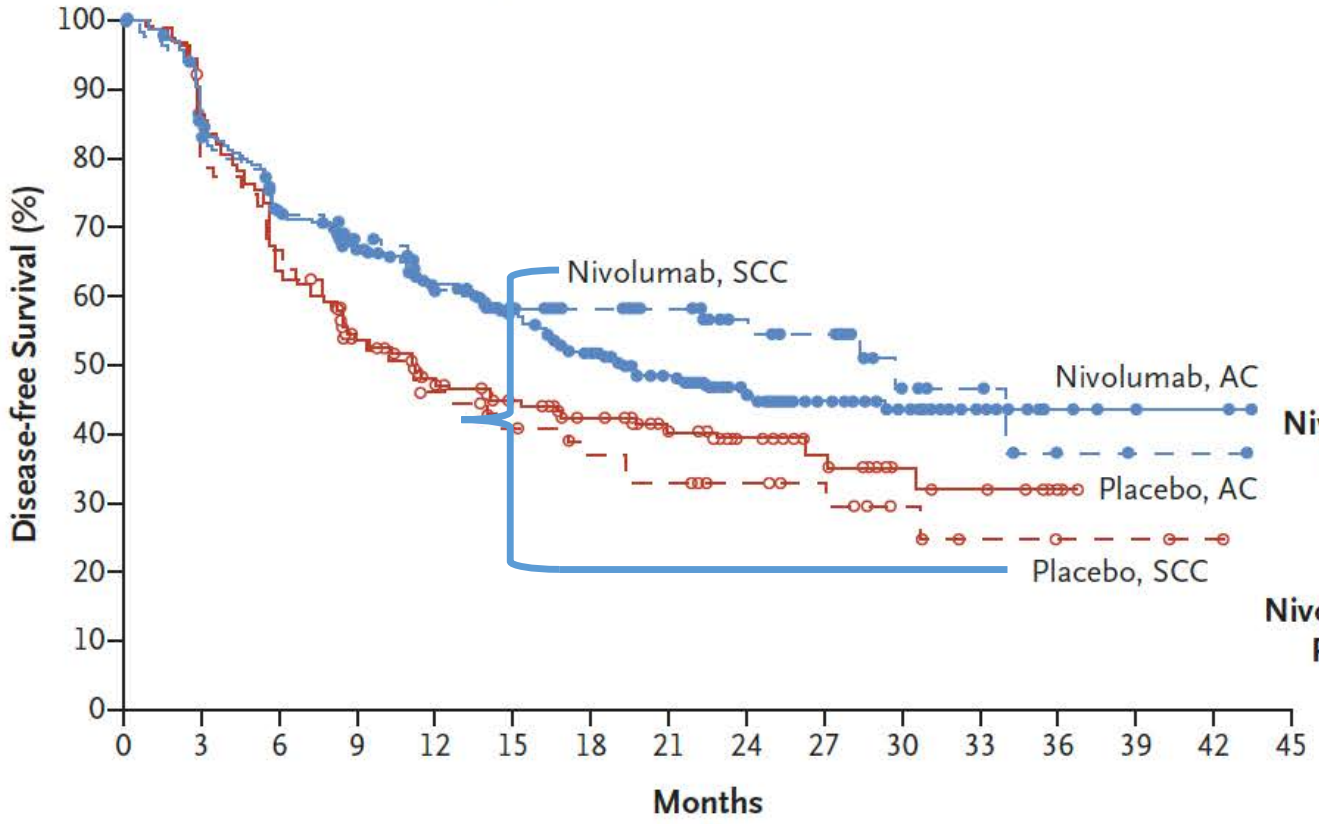
	No. of Patients	Median Disease-free Survival
		mo (95% CI)
Nivolumab	532	22.4 (16.6–34.0)
Placebo	262	11.0 (8.3–14.3)

Hazard ratio for disease recurrence or death, 0.69 (96.4% CI, 0.56–0.86)
P<0.001

Kelly, NEJM 2021

Checkmate-577: DFS by histology

B Disease-free Survival According to Histologic Type



	No. of Patients	Median Disease-free Survival
		mo (95% CI)
Nivolumab, AC	376	19.4 (15.9–29.4)
Placebo, AC	187	11.1 (8.3–16.8)
Hazard ratio for disease recurrence or death, 0.75 (95% CI, 0.59–0.96)		
Nivolumab, SCC	155	29.7 (14.4–NE)
Placebo, SCC	75	11.0 (7.6–17.8)
Hazard ratio for disease recurrence or death, 0.61 (95% CI, 0.42–0.88)		

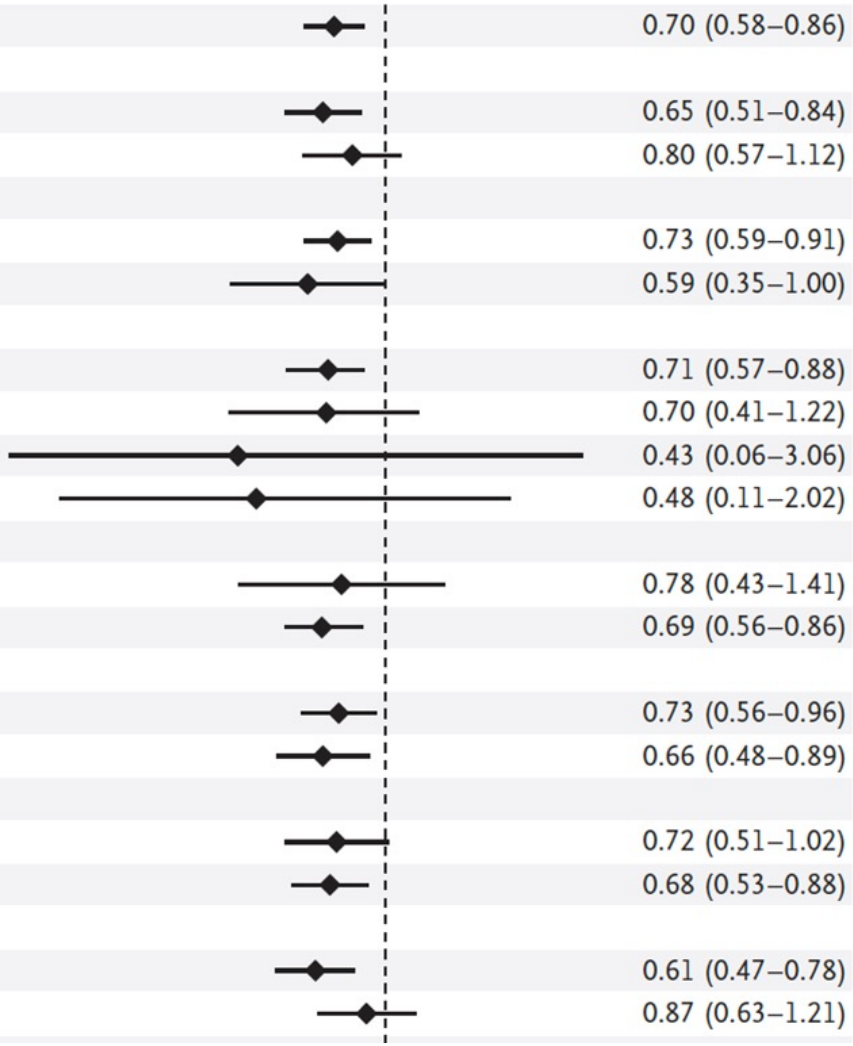
No. at Risk

Nivolumab, AC	376	305	257	219	178	151	125	99	65	45	32	16	6	3	2	0
Nivolumab, SCC	155	124	106	87	71	61	56	48	27	23	9	6	2	1	1	0
Placebo, AC	187	156	114	92	68	57	47	37	26	18	11	9	3	0	0	0
Placebo, SCC	75	58	49	34	28	23	18	16	12	10	6	3	2	2	1	0

Kelly, NEJM 2021

Checkmate-577: Forest Plot

Subgroup	No. of Patients	Median Disease-free Survival (mo)		Unstratified Hazard Ratio (95% CI)
		Nivolumab	Placebo	
Overall	794	22.4	11.0	0.70 (0.58–0.86)
Age				
<65 yr	507	24.4	10.8	0.65 (0.51–0.84)
≥65 yr	287	17.0	13.9	0.80 (0.57–1.12)
Sex				
Male	671	21.4	11.1	0.73 (0.59–0.91)
Female	123	Not reached	11.0	0.59 (0.35–1.00)
Race				
White	648	21.3	10.9	0.71 (0.57–0.88)
Asian	117	24.0	10.2	0.70 (0.41–1.22)
Black	9	14.4	8.3	0.43 (0.06–3.06)
Other	20	Not reached	14.1	0.48 (0.11–2.02)
Region				
Asia	106	24.0	14.3	0.78 (0.43–1.41)
Other	688	21.4	11.0	0.69 (0.56–0.86)
ECOG performance-status score				
0	464	29.4	11.1	0.73 (0.56–0.96)
1	330	17.0	10.9	0.66 (0.48–0.89)
Disease stage at initial diagnosis				
II	278	34.0	13.9	0.72 (0.51–1.02)
III	514	19.4	8.5	0.68 (0.53–0.88)
Tumor location at initial diagnosis				
Esophagus	462	24.0	8.3	0.61 (0.47–0.78)
Gastroesophageal junction	332	22.4	20.6	0.87 (0.63–1.21)



Kelly, NEJM 2021

Checkmate-577: Adverse Events

Treatment-related adverse events with potential immunologic etiology

Select TRAEs,[b,c] n (%)	Nivolumab[a] n = 532		Placebo[a] n = 260	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Endocrine	93 (17)	5 (< 1)	6 (2)	0
Gastrointestinal	91 (17)	4 (< 1)	40 (15)	3 (1)
Hepatic	49 (9)	6 (1)	18 (7)	4 (2)
Pulmonary	23 (4)	6 (1)	4 (2)	1 (< 1)
Renal	7 (1)	1 (< 1)	2 (< 1)	0
Skin	130 (24)	7 (1)	28 (11)	1 (< 1)

- The majority of select TRAEs were grade 1 or 2
- Grade 3-4 select TRAEs occurred in ≤ 1% of patients in the nivolumab arm and there were no grade 5 select TRAEs
- The most common grade 3-4 select TRAEs in the nivolumab arm were pneumonitis (n = 4) and rash (n = 4) (0.8% each); in the placebo arm, these events occurred in 1 patient each (0.4%)

Kelly, NEJM 2021

Example Case: Metastatic disease

- 62-year-old patient presents with dysphagia. EGD reveals a **GEJ mass** – biopsy reveals moderately-differentiated adenocarcinoma, pMMR, Her2 IHC negative, CPS=1.

- CT c/a/p reveals multiple bilobar liver metastases.

- No other medical problems, patient is healthy and works part time.

- ECOG performance status = 1

- What is your initial recommendation for therapy?
  - ECF
  - FOLFOX
  - FOLFOX/Nivo
  - FOLFOX/Pembro

Therapy options in advanced gastric/ esophageal cancers

1st Line	Fluoropyrimidine + platinum
	+Trastuzumab/Pembro (HER-2 positive)
	+Pembro (PD-L1 CPS ≥10)
	+Nivo (PD-L1 CPS ≥5)
2nd Line	Ramucirumab + paclitaxel
	Trastuzumab Deruxtecan (HER-2 positive)
	Pembro (MSI/MMR-D)
	Pembro (PD-L1 CPS ≥10)
3rd Line and beyond	Irinotecan
	Trifluridine/Tipiracil

1. National Comprehensive Cancer Network. Esophageal Cancer Guidelines v4.2021. Available at www.nccn.org. Accessed Sept 15, 2021
2. National Comprehensive Cancer Network. Gastric Cancer Guidelines v4.2021. Available at www.nccn.org. Accessed Sept 15, 2021

Combination chemotherapy results in improved survival

Study	Treatment	No Pts	RR (%)	TTP (mos)	OS (mos)	P-value
Van Cutsem (V325)	CDDP+5FU	224	25	3.7	**8.6**	**0.02**
	Doce+CDDP+5FU	221	37	5.6	**9.2**	
Dank (V306)	CDDP+5FU	163	26	4.2	**8.7**	**NS**
	Irinotecan+5FU/LV	170	32	5.0	**9.0**	
Cunningham (REAL-2)	ECF	263	41	6.2	**9.9**	**0.02**
	EOF	245	42	6.5	**9.3**	
	ECX	250	46	6.7	**9.9**	
	EOX	244	48	7.0	**11.2**	
Kang	CDDP+5FU	137	29	5.0	**9.3**	**NS**
	CDDP+**capecitabine**	139	41	5.6	**10.5**	
Boku (JCDG9912)	5FU	234	9	2.9	**10.8**	**NS**
	CDDP+**irinotecan**	236	38	4.8	**12.3**	
	S-1	234	28	4.2	**11.4**	
Narahara (SPIRITS)	**S-1**	150	31	4.0	**11.0**	**0.036**
	CDDP+**S-1**	148	54	6.0	**13.0**	
Ajani (FLAGS)	CDDP+5-FU	508	31.9	5.5	**7.9**	**0.0198**
	CDDP+**S-1**	521	29.1	4.8	**8.6**	

Courtesy of S. Kim, Colorado

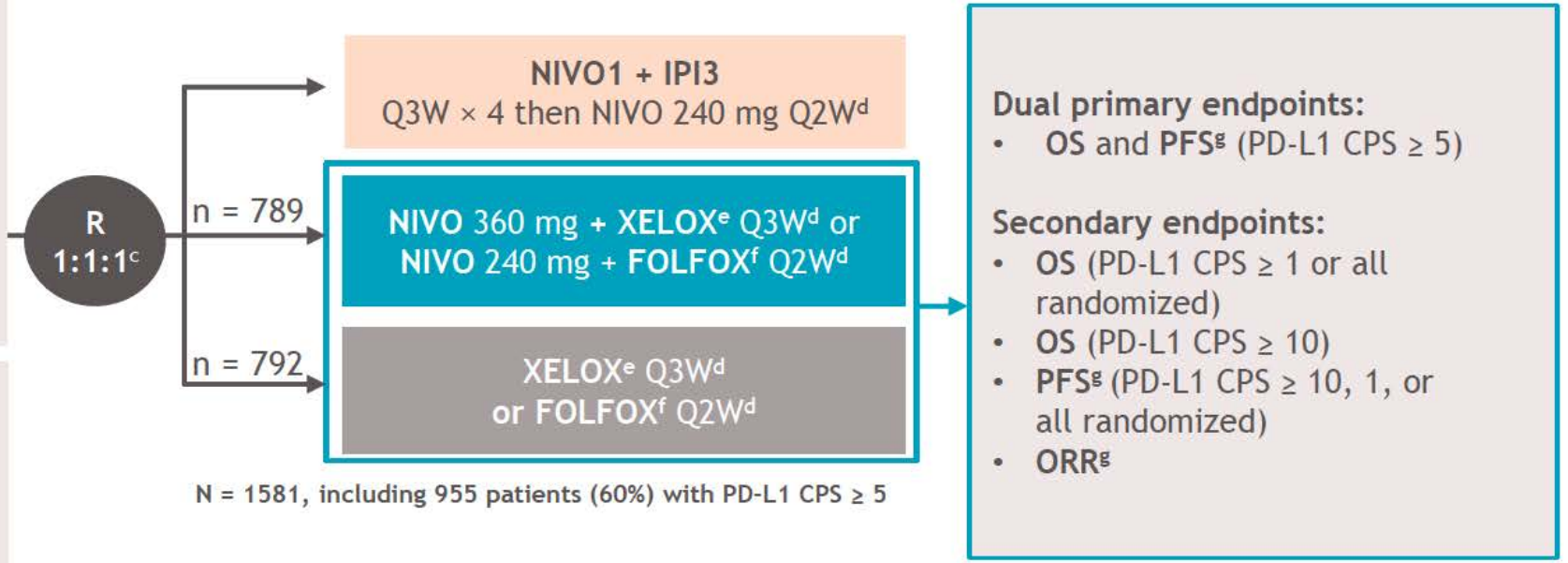
CheckMate 649: 1L Chemoimmunotherapy in gastric and GEJ

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)

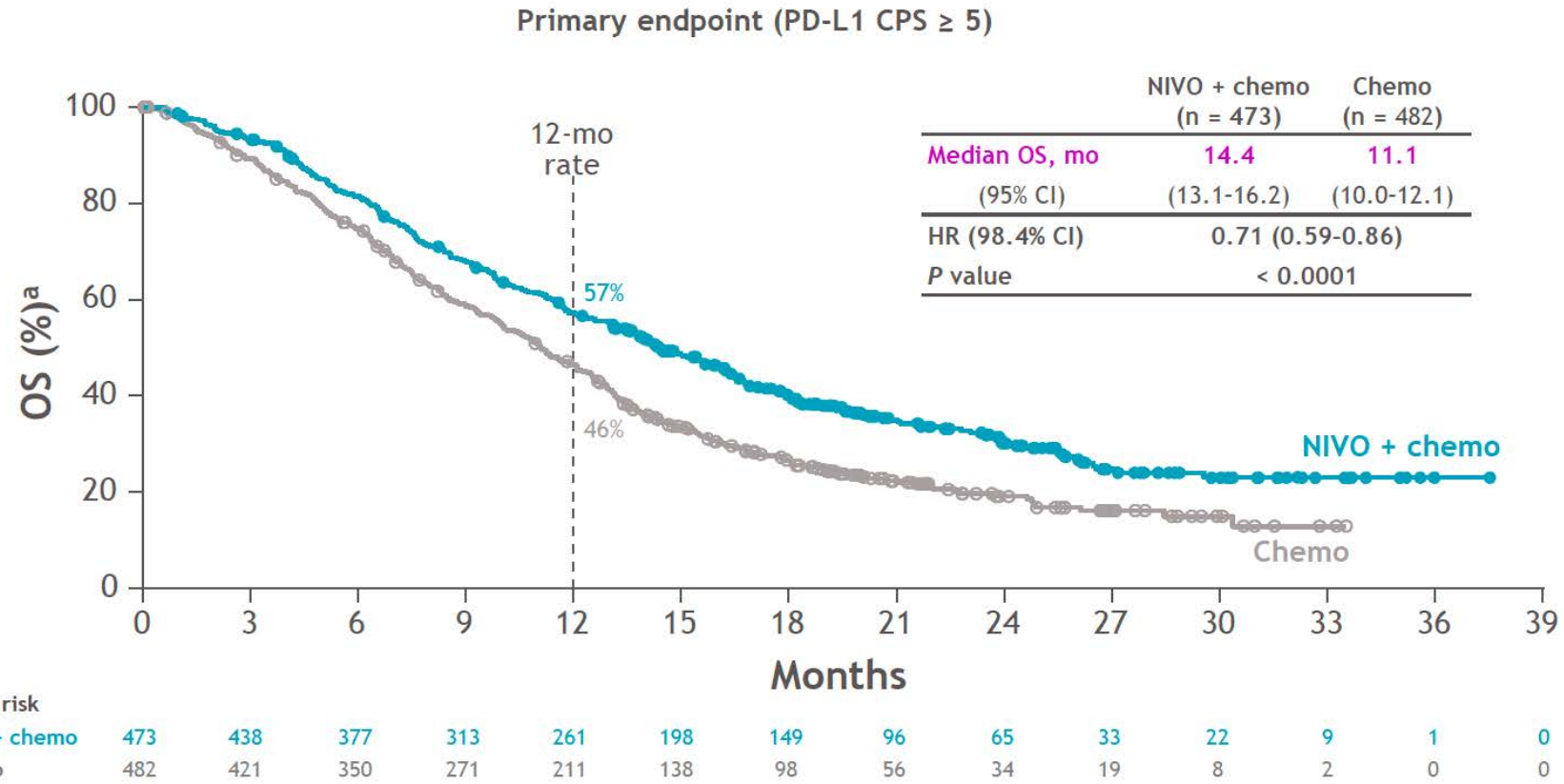


- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

Janjigian, Lancet 2021

CheckMate 649: 1L Chemoimmunotherapy

Overall survival



- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5

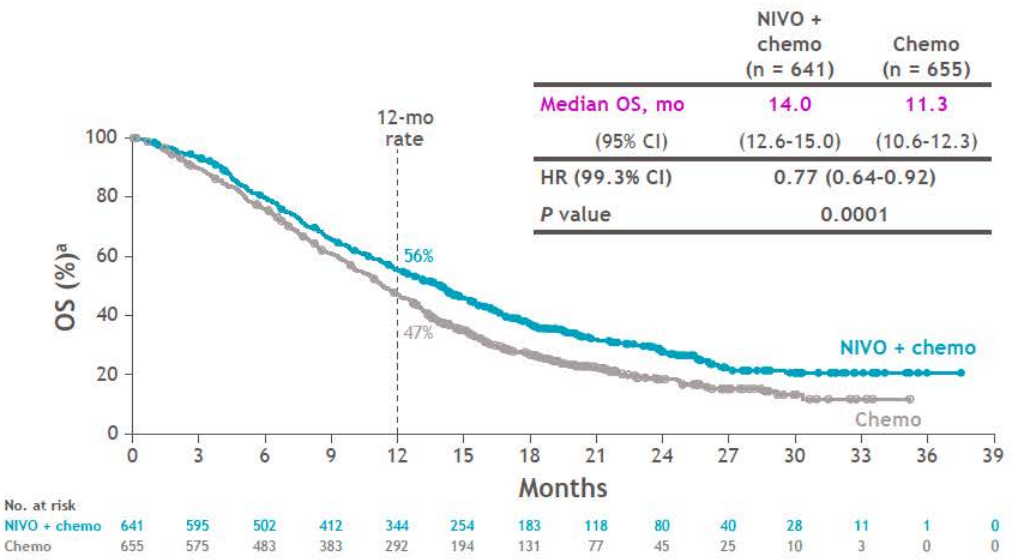
[a]Minimum follow-up 12.1 months.

Janjigian, Lancet 2021

CheckMate 649: 1L Chemoimmunotherapy in gastric and GEJ

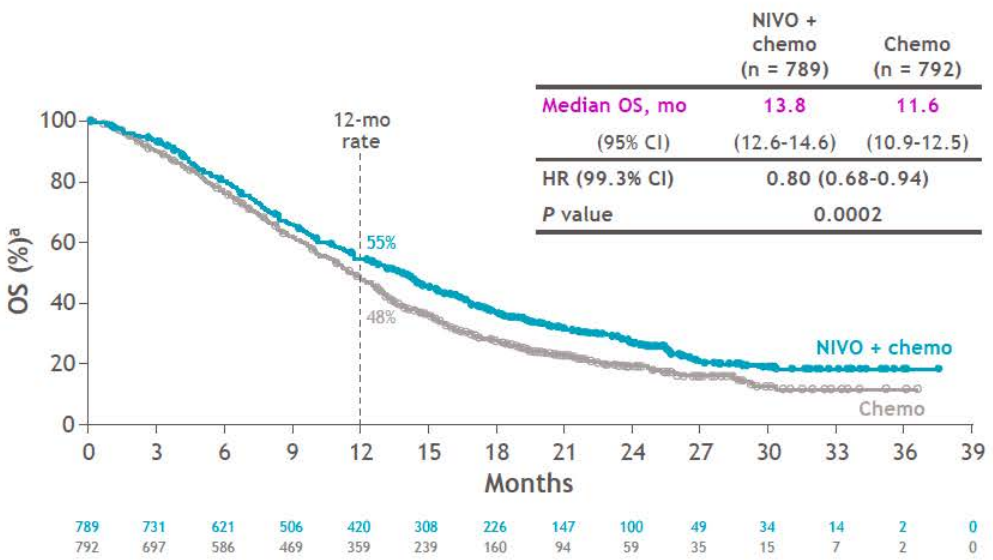
Overall survival

PD-L1 CPS ≥ 1



74% CPS ≥ 5

All randomized



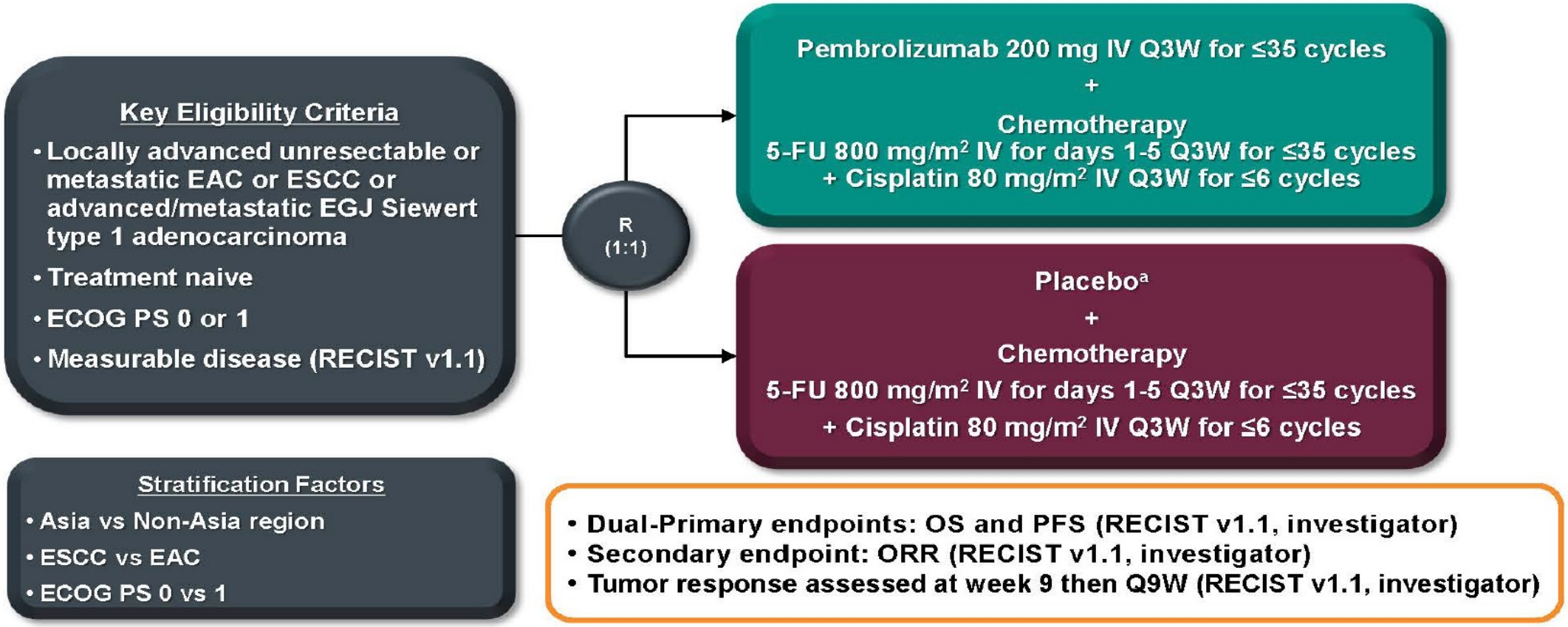
60% CPS ≥ 5

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

Janjigian, Lancet 2021

Keynote-590: 1L Chemoimmunotherapy

KEYNOTE-590 Study Design (NCT03189719)



Primary end points were
- OS in pts with ESCC PD-L1 combined positive score (CPS) ≥10 tumors
- OS and PFS in ESCC, PD-L1 CPS ≥10, and all pts.

Sun, Lancet 2021

Keynote-590: 1L Chemoimmunotherapy

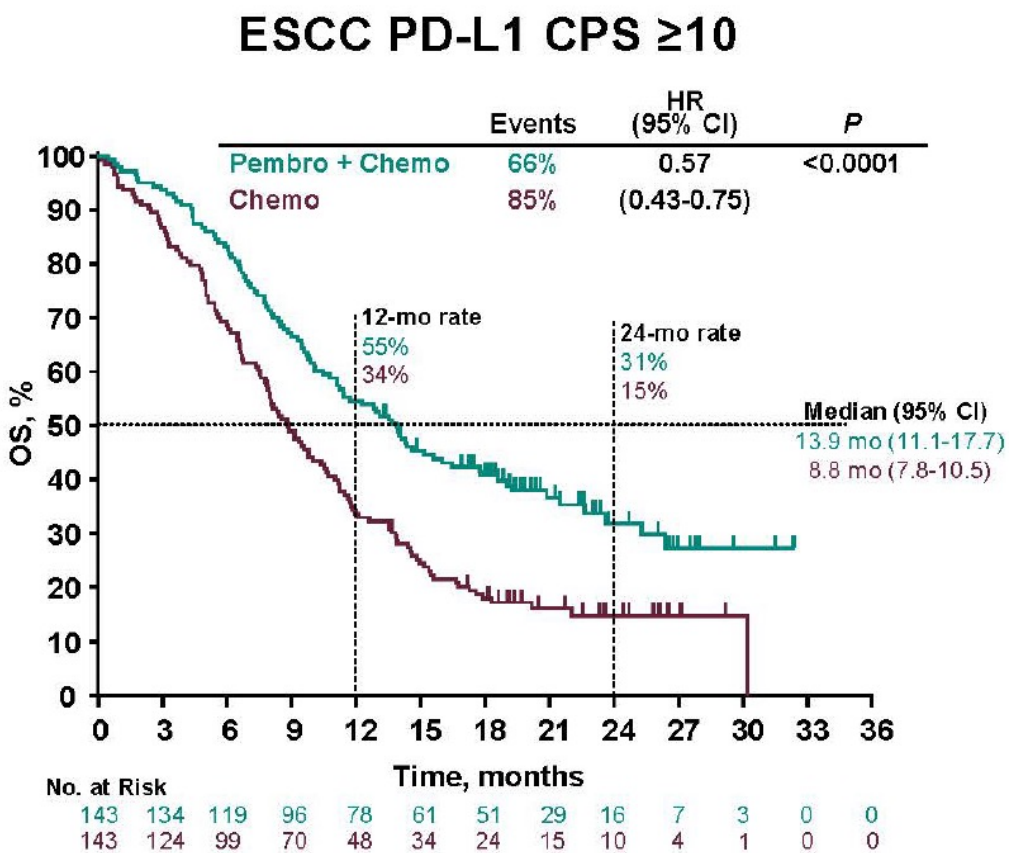
Baseline Characteristics (ITT)

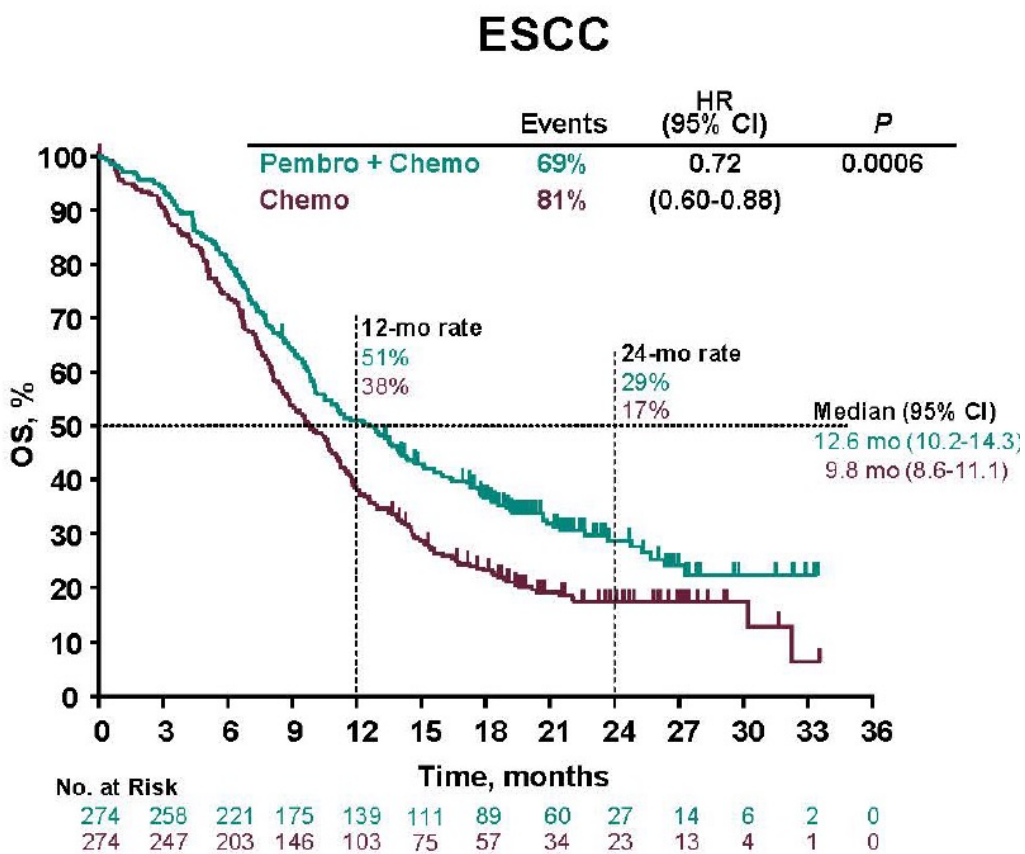
Characteristic, n (%)	Pembro + Chemo N = 373	Chemo N = 376
Median age, years (range)	64.0 (28-94)	62.0 (27-89)
≥65 years	172 (46)	150 (40)
Male	306 (82.0)	319 (84.8)
Asia Region	196 (52.5)	197 (52.4)
ECOG PS 1	223 (59.8)	225 (59.8)
Metastatic disease	344 (92.2)	339 (90.2)
Unresectable/locally-advanced	29 (7.8)	37 (9.8)
Squamous-cell carcinoma	274 (73.5)	274 (72.9)
Adenocarcinoma	99 (26.5)	102 (27.1)
Esophageal	58 (15.5)	52 (13.8)
EGJ	41 (11.0)	50 (13.3)
PD-L1 CPS ≥10[a]	186 (49.9)	197 (52.4)

Sun, Lancet 2021

Keynote-590: OS in SCC

Overall Survival



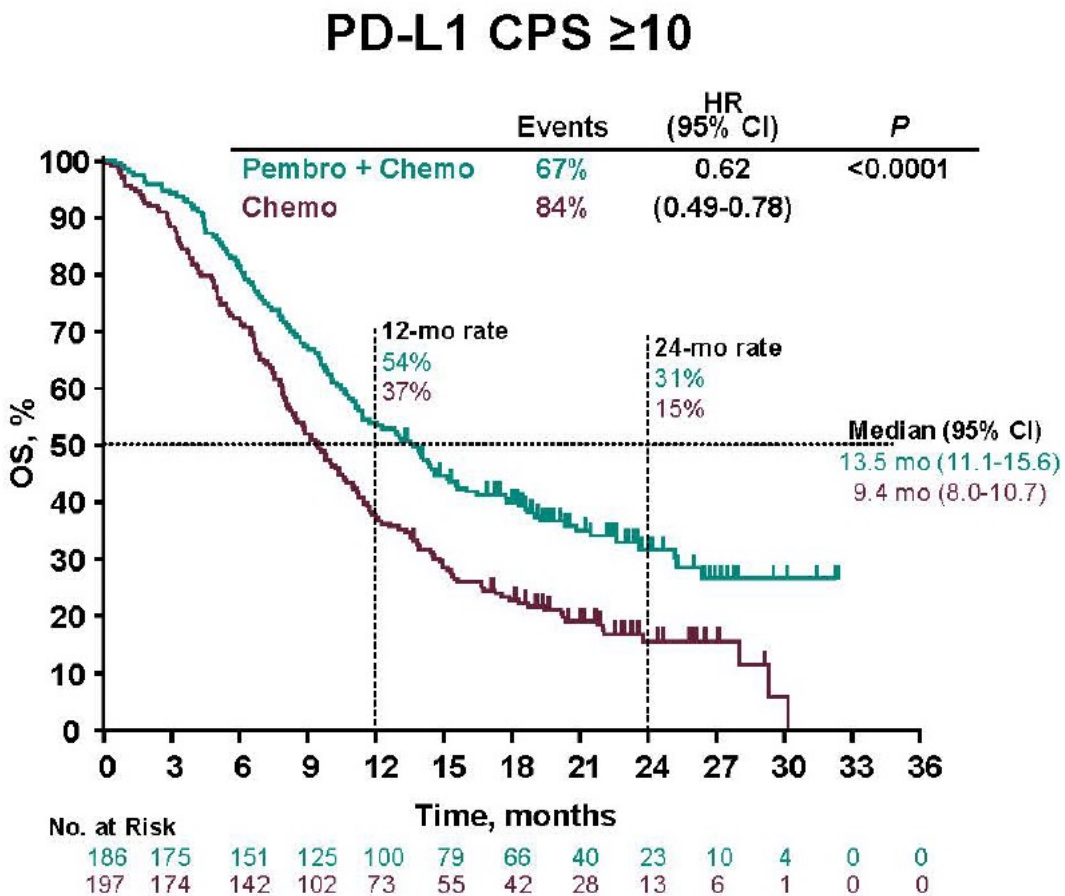


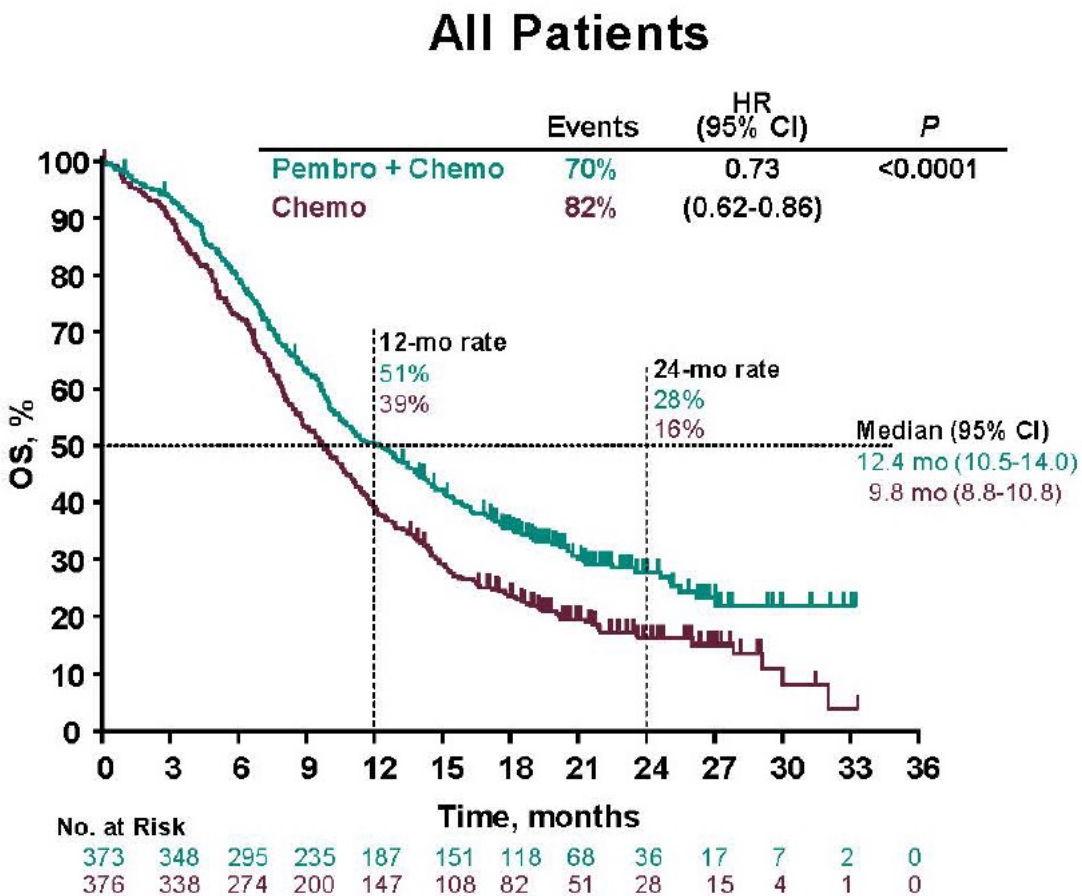
Data cut-off: July 2, 2020

Sun, Lancet 2021

Keynote-590: OS by CPS and All patients

Overall Survival





Sun, Lancet 2021

Questionable PD-L1 Assay Concordance

CPS cutoff	Proportion of samples testing PD-L1 positive, %		*P* value
	22C3	28-8	
≥ 1	49.4	70.3	< .001
≥ 5	13.4	29.1	< .001
≥ 10	7.0	13.7	.004

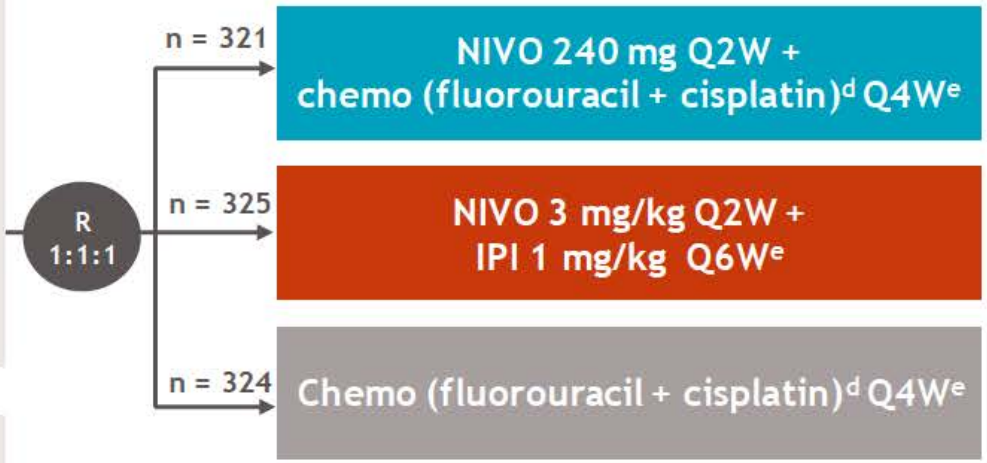
Different results with different antibodies.

Tay, 2022 Annual ASCO Meeting

CheckMate-648: esophageal SCC

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

Exploratory endpoints:
- OS (by tumor cell PD-L1 and PD-L1 CPS)
- DOR[f]
- PFS2[g]
- Safety

- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[h]

Chau, ESMO GI 2022

CheckMate-648: esophageal SCC

All randomized	NIVO + chemo (n = 321)	NIVO + IPI (n = 325)	Chemo (n = 324)[a]
Median age, years (range)	64 (40-90)	63 (28-81)	64 (26-81)
Male, %	79	83	85
Asian,[b] %	70	70	70
ECOG PS 1, %	53	54	52
ESCC,[c] %	97	> 99	98
Tumor cell PD-L1 expression,[d] %			
≥ 1%	49	49	48
≥ 5%	37	37	36
≥ 10%	32	32	30
Disease status at study entry, %			
De novo metastatic	57	60	58
Recurrent - locoregional	7	8	8
Recurrent - distant	22	22	19
Unresectable advanced	14	10	16
Number of organs with metastases[e]			
≤ 1	49	49	49
≥ 2	51	51	51
Current or former smoker, %	79	82	79

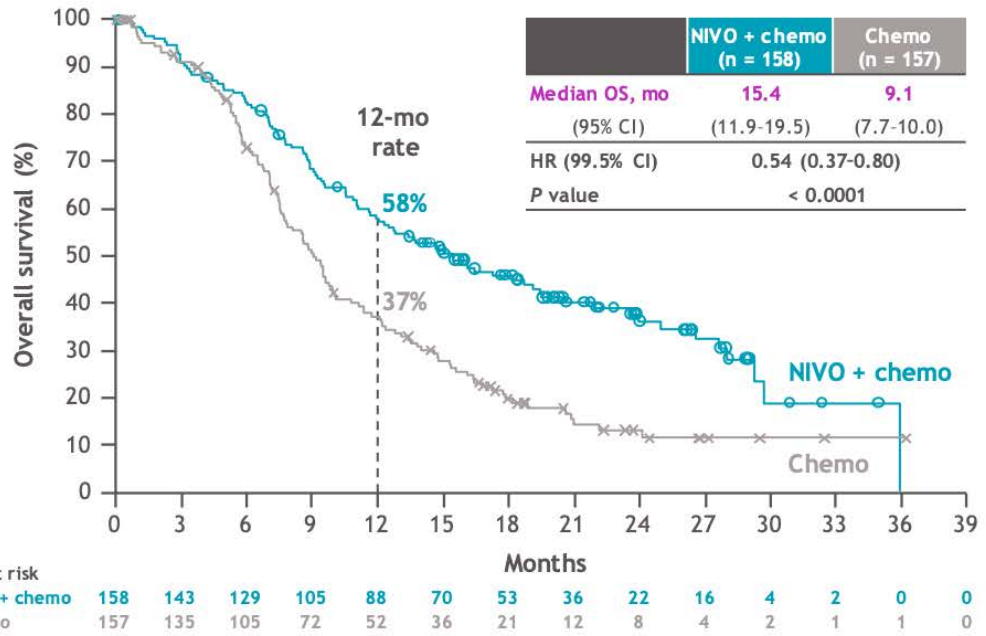
- Of the 906 patients with quantifiable PD-L1 expression at baseline across all three treatment arms, a total of 288 (32%) had both tumor cell PD-L1 ≥ 1% and PD-L1 CPS ≥ 10, and 339 (37%) had both tumor cell PD-L1 < 1% and PD-L1 CPS < 10

Chau, ESMO GI 2022

CheckMate-648: esophageal SCC

Overall survival: NIVO + chemo vs chemo

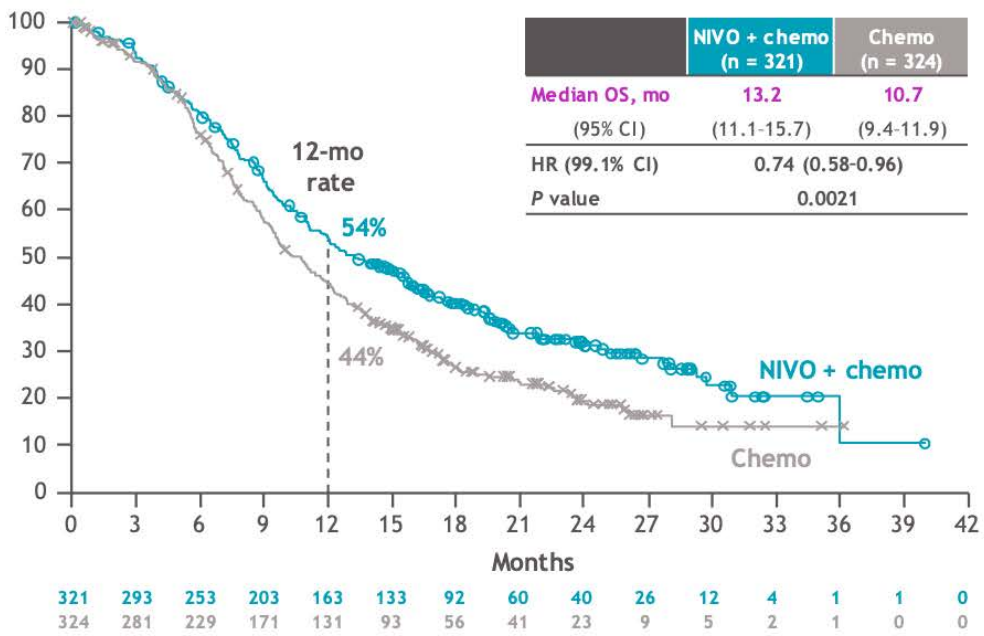
Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



	NIVO + chemo (n = 158)	Chemo (n = 157)
Median OS, mo	15.4	9.1
(95% CI)	(11.9-19.5)	(7.7-10.0)
HR (99.5% CI)	0.54 (0.37-0.80)	
P value	< 0.0001	

No. at risk														
NIVO + chemo	158	143	129	105	88	70	53	36	22	16	4	2	0	0
Chemo	157	135	105	72	52	36	21	12	8	4	2	1	1	0

All randomized[a]



	NIVO + chemo (n = 321)	Chemo (n = 324)
Median OS, mo	13.2	10.7
(95% CI)	(11.1-15.7)	(9.4-11.9)
HR (99.1% CI)	0.74 (0.58-0.96)	
P value	0.0021	

321	293	253	203	163	133	92	60	40	26	12	4	1	1	0
324	281	229	171	131	93	56	41	23	9	5	2	1	0	0

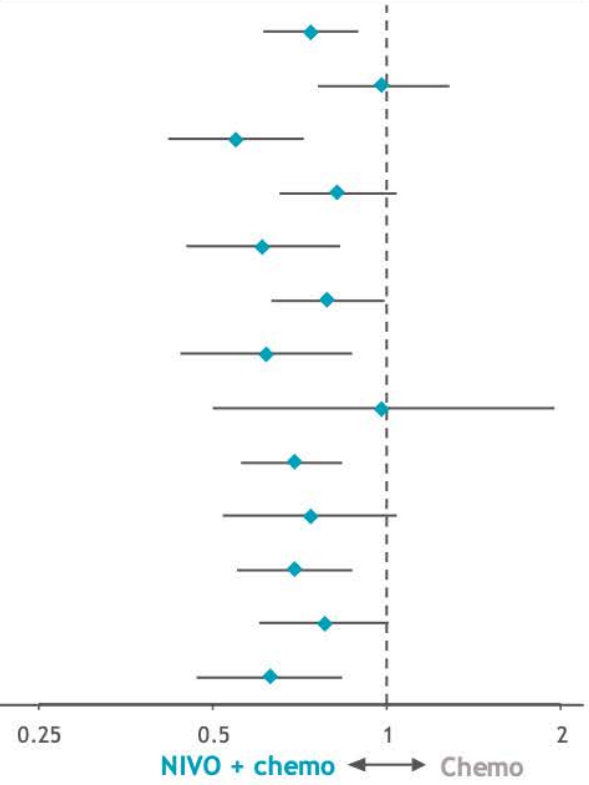
- Superior OS with NIVO + chemo vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 46% reduction in the risk of death and a 6.3-month improvement in median OS
  - All randomized: 26% reduction in the risk of death and a 2.5-month improvement in median OS

Chau, ESMO GI 2022

CheckMate-648: esophageal SCC

Overall survival by baseline PD-L1 status: NIVO + chemo vs chemo

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 645)		13.2	10.7	0.74	
Tumor cell PD-L1 expression[a]	< 1% (n = 329)	12.0	12.2	0.98	
	≥ 1% (n = 314)	15.4	9.2	0.55	
	< 5% (n = 408)	12.8	11.1	0.82	
	≥ 5% (n = 235)	13.7	9.5	0.61	
	< 10% (n = 444)	12.3	10.8	0.79	
	≥ 10% (n = 199)	14.7	9.5	0.62	
PD-L1 CPS[b,c]	< 1 (n = 51)	9.9	12.1	0.98	
	≥ 1 (n = 558)	13.8	9.8	0.69	
	< 5 (n = 188)	12.0	9.4	0.74	
	≥ 5 (n = 421)	15.2	11.1	0.69	
	< 10 (n = 329)	12.1	9.7	0.78	
	≥ 10 (n = 280)	16.1	11.6	0.63	



Chau, ESMO GI 2022

Summary of Adjuvant/1L Trials in Gastric/GEJ

- Early gastric/esophageal cancer should be treated with a multimodality treatment
  - Esophageal: chemoradiation->surgery->adjuvant nivolumab
  - Gastric: chemo->surgery->chemo

- 1L Therapy Recommendations
  - ESCC CPS $\geq$ 10
    - Chemo + pembro
  - Gastric and GEJ/Esophageal AC CPS $\geq$ 5
    - Chemo + nivo

- NO significant difference in mOS in low PD-L1 CPS groups in CheckMate-649 and KEYNOTE-590

- For borderline PD-L1 CPS (e.g. CPS 4 for gastric or CPS 9 for esophageal SCC), use clinical judgement

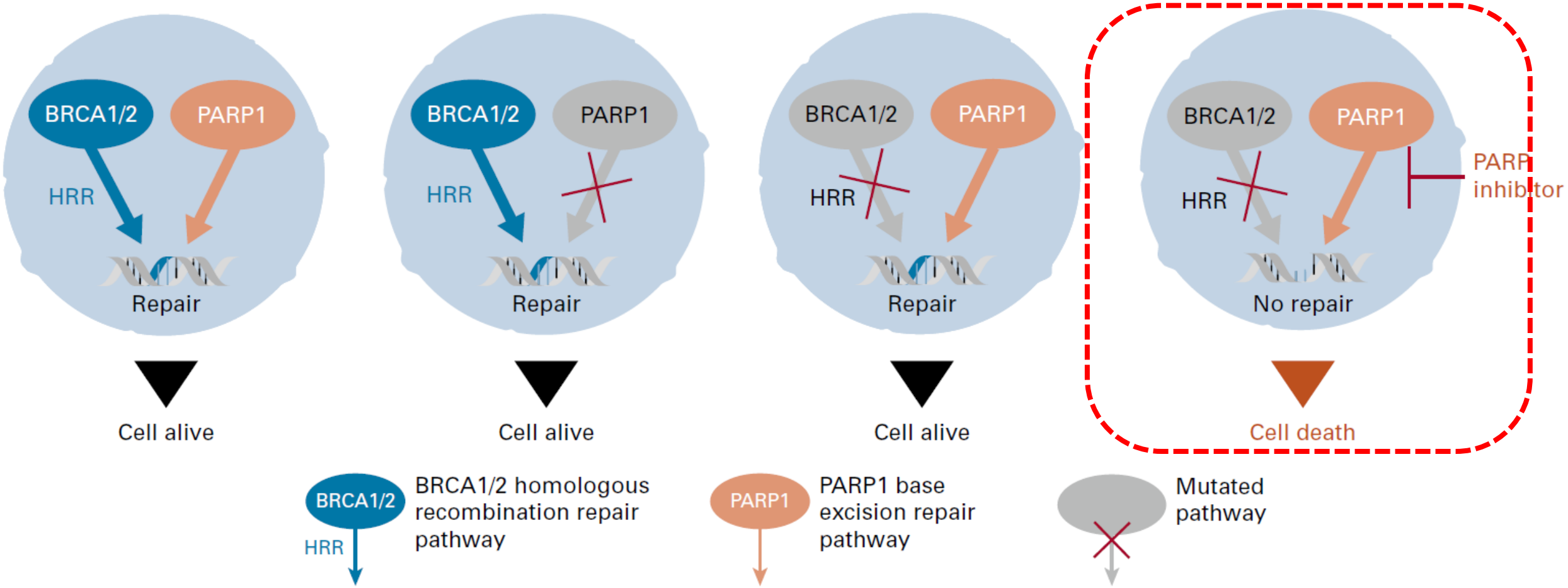
- New biomarker directed trials/results may again change landscape
  - FGFR2, CLDN18.2

PARPi in Pancreatic Cancer

Example Case

- 58-yr-old woman with no family history of cancer presented with pelvic pain
- Workup revealed metastatic pancreatic cancer with diffuse liver metastases; germline testing showed no inherited mutations
- She started first-line FOLFIRINOX and was able to complete 8 cycles of treatment with dose adjustments despite it being poorly tolerated
- Somatic tumor testing revealed a BRCA2 mutation; results returned during cycle 2 of FOLFIRINOX
- Her disease burden improved after 8 cycles of FOLFIRINOX

- What is your recommendation for next steps:
  - Continue FOLFIRINOX
  - Stop FOLFIRINOX and observe
  - PARPi maintenance therapy (note: FDA approved for germline)
  - 5-FU/capecitabine maintenance therapy



PARP poly (ADP-ribose) polymerase

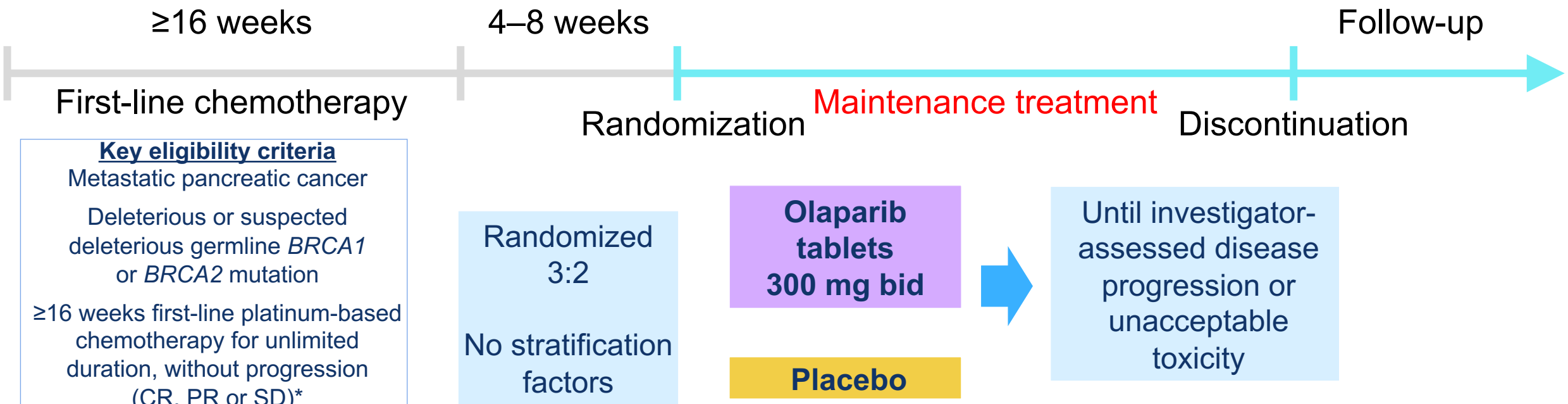
HRR homologous recombination repair

BRCA BReast CAncer gene

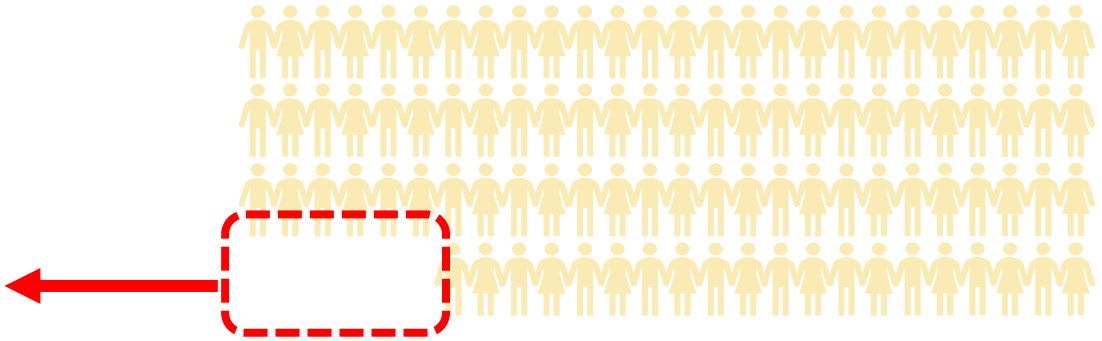
In the setting of deficient BRCA1/2, PARP inhibition causes deficient DNA repair and cell death.

Gourley, *J Clin Oncol* 2019

Study design: Subset of a small subset



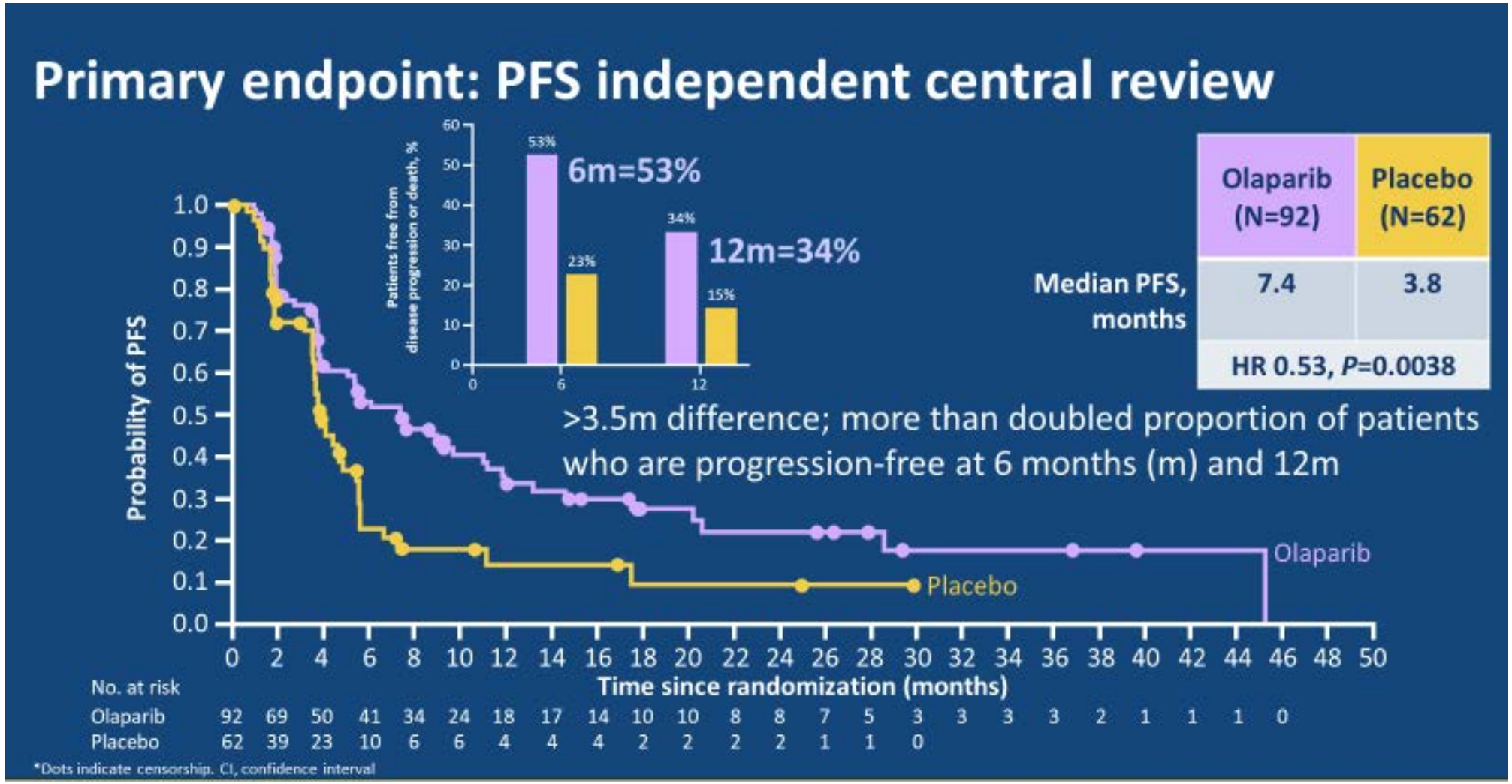
Screened 3315 to find 247 (93 excluded)



38% of gBRCAm patients had disease progression, were ineligible, or declined randomization.

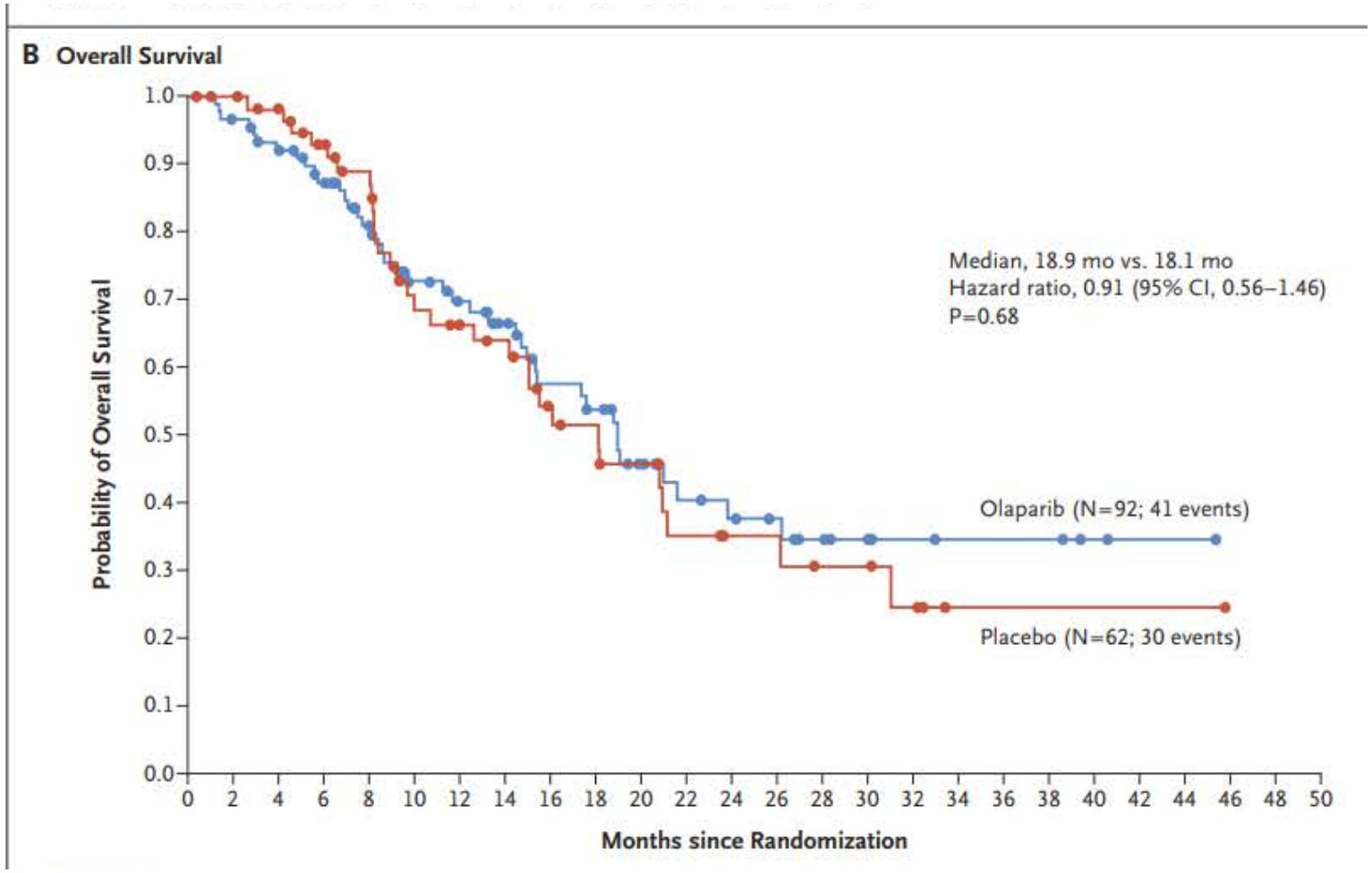
Messersmith, ASCO 2019

POLO: Maintenance Olaparib vs Placebo After First-line Platinum-Based Therapy in Metastatic Pancreatic Cancer



Golan. NEJM. 2019;381:317. Golan. ASCO GI 2021. Abstr 378.

POLO: No Difference in Overall Survival



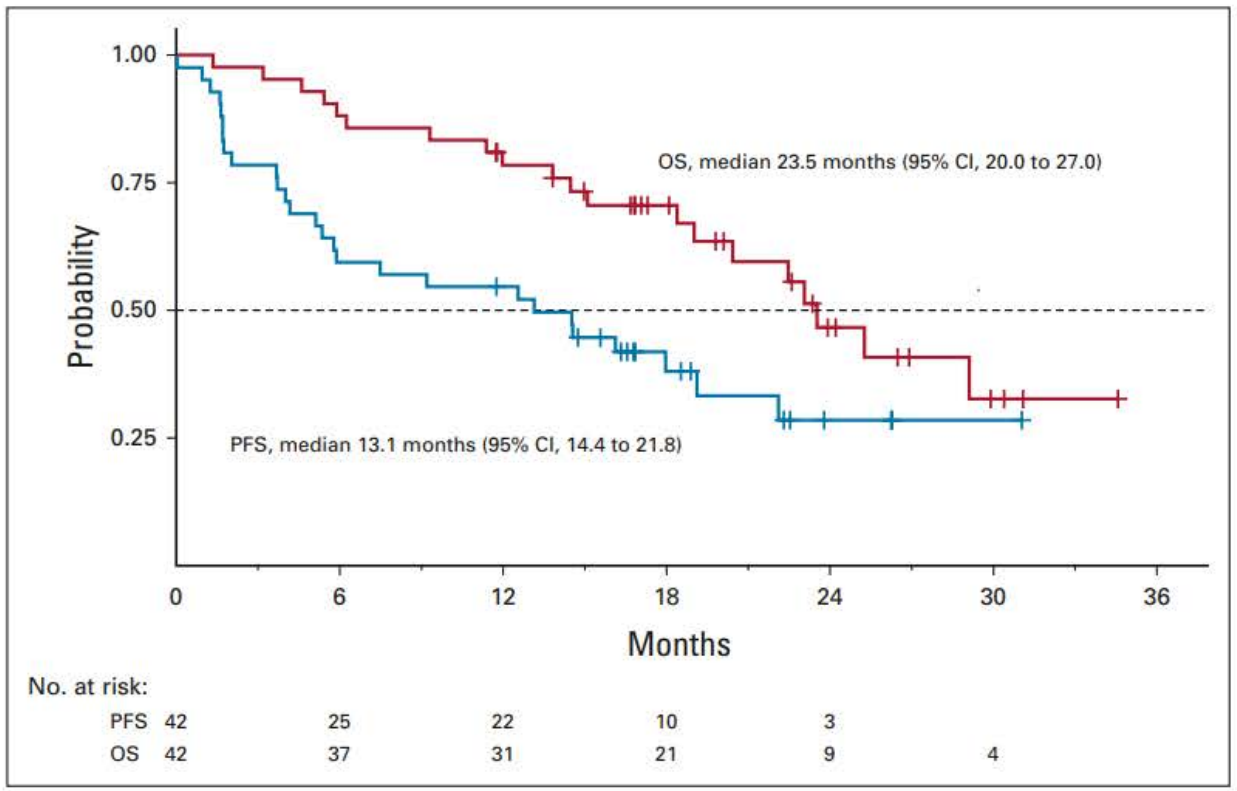
NEJM: only nine patients in the placebo group (15%) who went on to receive a PARP inhibitor after disease progression during the trial intervention.
(low crossover rate)

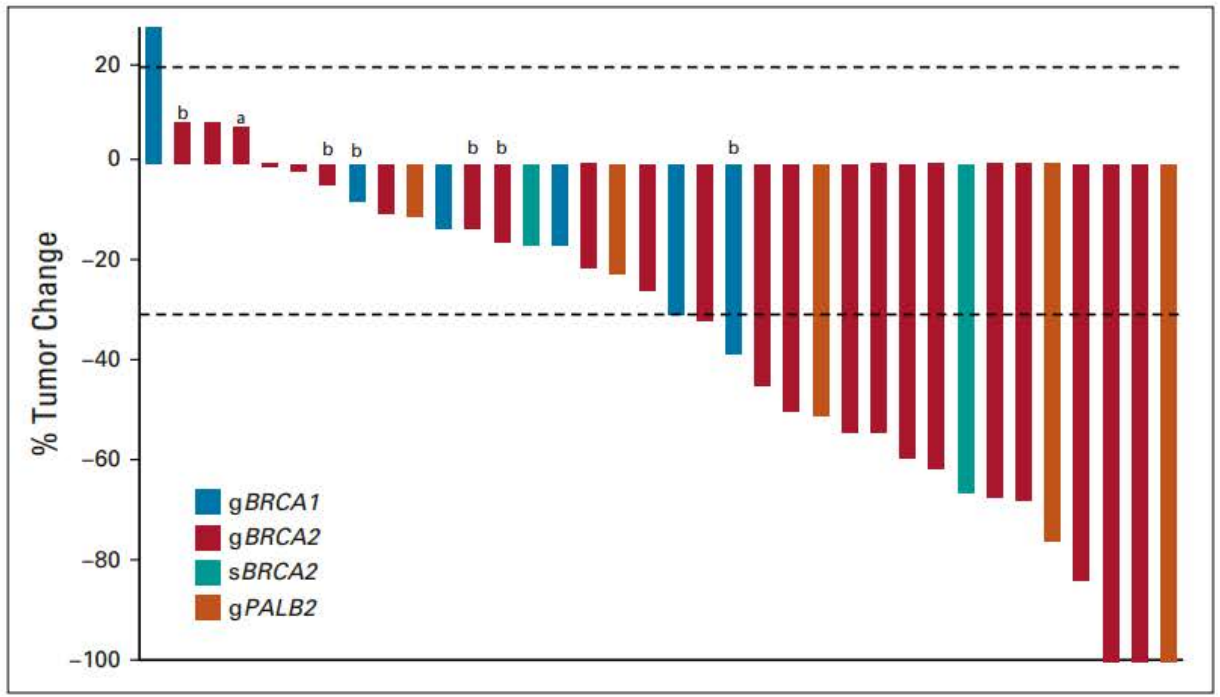
Golan, NEJM 2019

original reports

Phase II Study of Maintenance Rucaparib in Patients With Platinum-Sensitive Advanced Pancreatic Cancer and a Pathogenic Germline or Somatic Variant in *BRCA1*, *BRCA2*, or *PALB2*

Kim A. Reiss, MD[1,2]; Rosemarie Mick, MS[1,3]; Mark H. O'Hara, MD[1,2]; Ursina Teitelbaum, MD[1,2]; Thomas B. Karasic, MD[1,2];

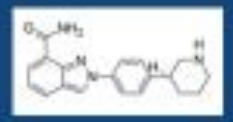


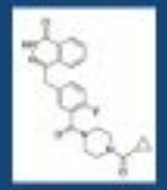


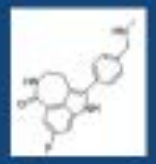
Reiss, JCO 2021

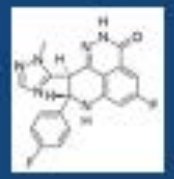
Approximate Costs of PARP inhibitors

AWP pricing for the standard FDA approved doses: one month of therapy

Niraparib 
300 mg (3 x 100 mg) orally daily
AWP for 90 capsules $20,072, $223/capsule

Olaparib 
300 mg (2 x 150 mg) orally twice daily
AWP for 120 tablets $16,830, $140/tablet

Rucaparib 
600 mg (2 x 300 mg) orally twice daily
AWP for 120 tablets $19,106, $159/tablet

Talazoparib 
1 mg (1 x 1 mg) orally once daily
AWP for 30 capsules $17,496, $583/capsule

POLO Study: 7.4 months of (median) progression-free survival would cost ~$124,540

Cindy L. O'Bryant, PharmD; Professor, University of Colorado Skaggs School of Pharmacy Pharmaceutical Sciences
Source: Institute for Clinical and Economic Review, https://icer-review.org

Messersmith, ASCO 2019

Key Points for BRCA mutated pancreatic cancer

Olaparib is FDA-approved as a maintenance therapy in germline mutated BRCA pancreatic cancer patients.

Unclear if simply continuing chemo would also work as well.

PARPi also have activity in patients with somatic BRCA mutations (not FDA approved)

Ongoing combination studies.

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Thank you!

Checkpoint Inhibitor Approvals for HER2-Negative Gastric, GEJ and Esophageal Cancers

Regimen/FDA approval date/pivotal trial	Location	Histology	Setting	PD-L1
Nivolumab 5/20/21 (CM-577)	Esophageal, GEJ	Adenocarcinoma and squamous	• Completed resection, with residual pathologic disease after neoadjuvant chemoradiation	Not required
Pembrolizumab + cisplatin/5-FU 3/22/2021 (KN-590)	Esophageal, GEJ	Adenocarcinoma and squamous	• Recurrent locally advanced or metastatic • Not amenable to surgical resection or definitive chemoradiation	Not required
Nivolumab + mFOLFOX6 or CAPOX 4/16/2021 (CM-649)	Gastric, GEJ, esophageal	Adenocarcinoma	• Advanced or metastatic gastric, GEJ or esophageal adenocarcinoma	Not required
Pembrolizumab 7/30/2019 (KN-181)	Esophageal, GEJ	Squamous	• Recurrent locally advanced or metastatic • Not amenable to surgical resection or definitive chemoradiation • After ≥1 prior lines of systemic therapy	CPS ≥10
Nivolumab 6/10/2020 (ATTRACTION-3)	Esophageal	Squamous	• Unresectable advanced, recurrent or metastatic • After prior fluoropyrimidine- and platinum-based chemotherapy	Not required

GEJ = gastroesophageal junction; CPS = combined positive score

Kelly RJ et al. *New Engl J Med* 2021;384(13):1191-203. Sun J et al. *Lancet* 2021;398(10302):759-71. Janjigian YY et al. *Lancet* 2021;398(10294):27-40. Kojima T et al. *J Clin Oncol* 2020;38(35):4138-48. Kato K et al. *Lancet Oncol* 2019;20(11):1506-17.

2021 ASCO ANNUAL MEETING

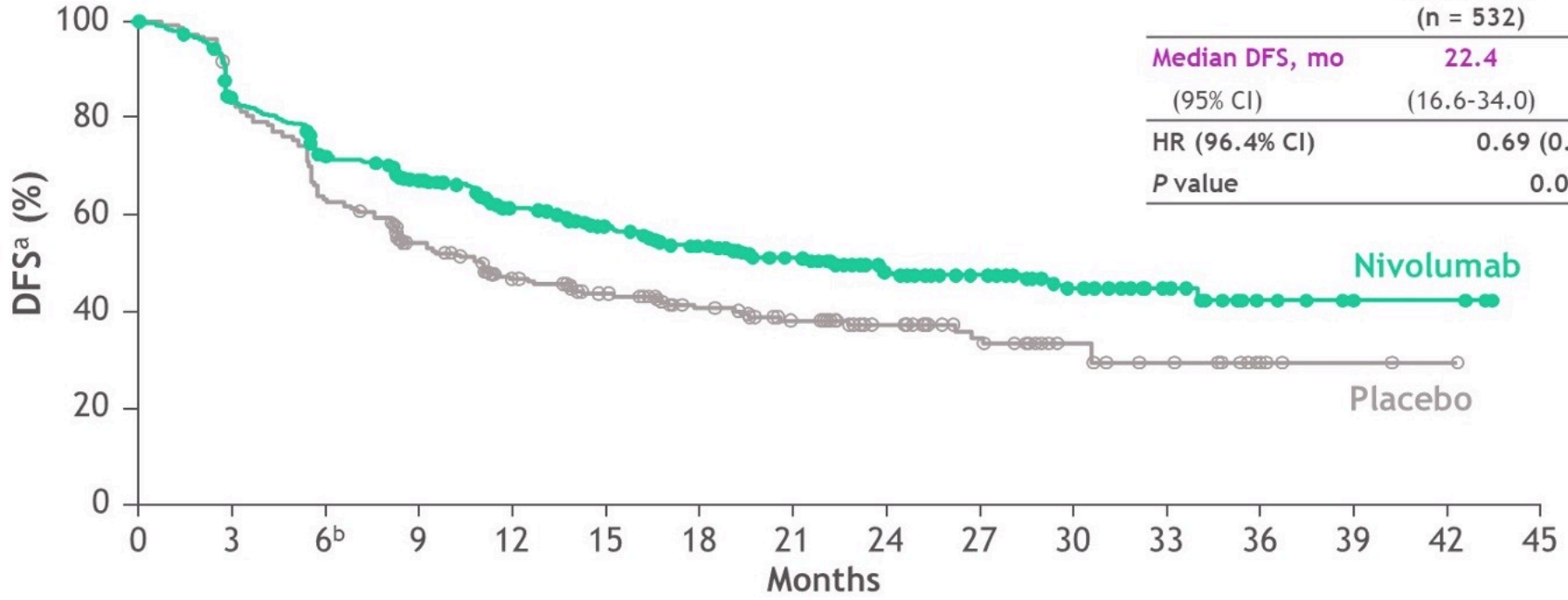
Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy: expanded efficacy and safety analyses from CheckMate 577

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] Samira Soleymani,[15] Ming Lei,[15] Prianka Singh,[15] James M. Cleary,[16] Markus Moehler[17]

[1]The Charles A. Sammons Cancer Center at Baylor University Medical Center, Dallas, TX; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [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; [9]Akita University Hospital, Akita, Japan; [10]CHU Pontchaillou, Rennes 1 University, Rennes, France; [11]Duke Cancer Institute, Durham, NC; [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; [16]Dana Farber Cancer Institute, Boston, MA; [17]Johannes-Gutenberg University Clinic, Mainz, Germany

Abstract number 4003

CheckMate 577: Disease-Free Survival (DFS)



	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6-34.0)	(8.3-14.3)
HR (96.4% CI)	0.69 (0.56-0.86)	
P value	0.0003[c]	

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

Kelly RJ et al. ASCO 2021;Abstract 4003.

RTP RESEARCH TO PRACTICE

Nature 2022 March;603(7903):942-8.

Article

Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer

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

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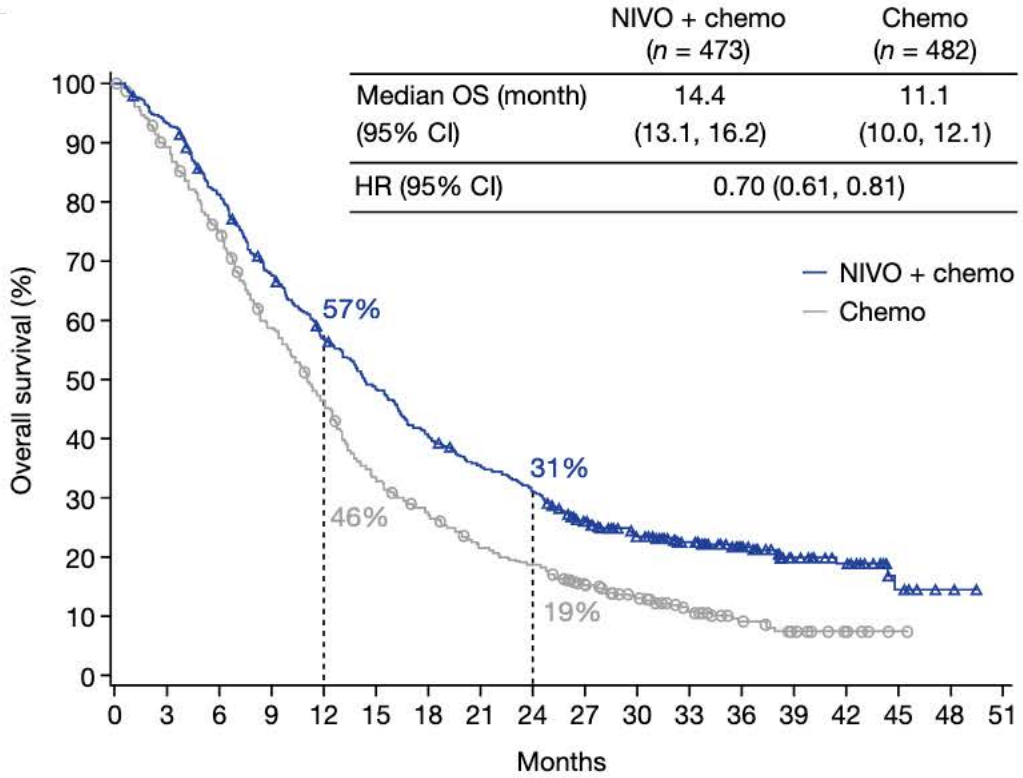
Open access

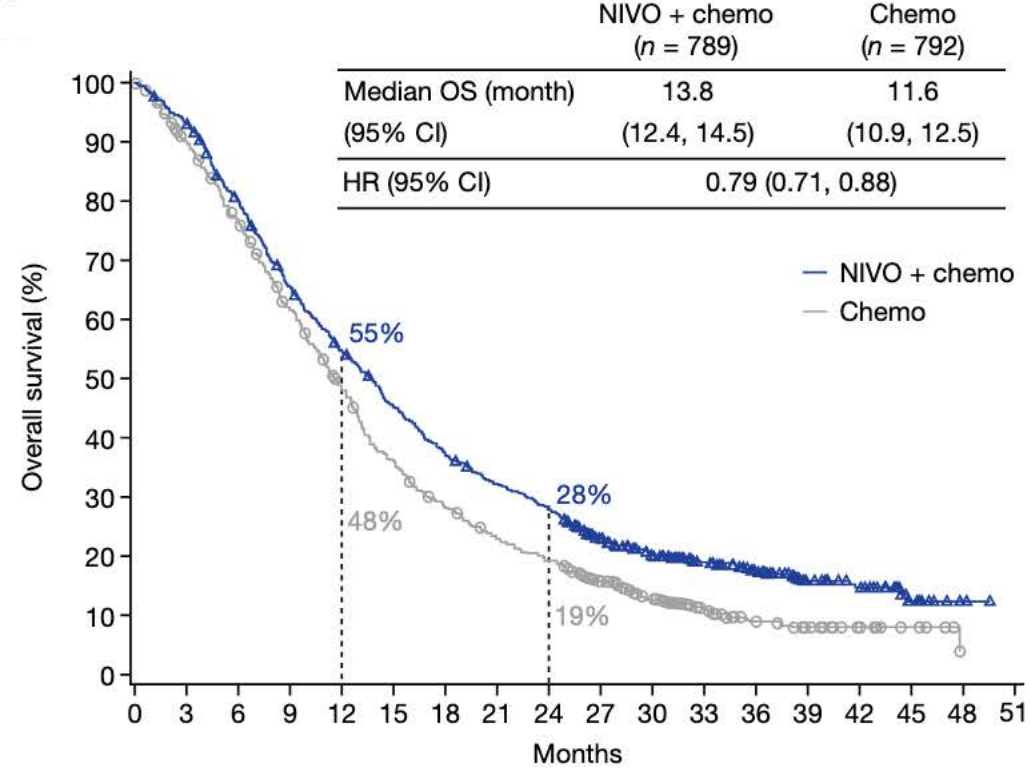
Kohei Shitara[1], Jaffer A. Ajani[2], Markus Moehler[3], Marcelo Garrido[4], Carlos Gallardo[5], Lin Shen[6], Kensei Yamaguchi[7], Lucjan Wyrwicz[8], Tomasz Skoczylas[9], Arinilda Campos Bragagnoli[10], Tianshu Liu[11], Mustapha Tehfe[12], Elena Elimova[13], Ricardo Bruges[14], Thomas Zander[15], Sergio de Azevedo[16], Ruben Kowalyszyn[17], Roberto Pazo-Cid[18], Michael Schenker[19], James M. Cleary[20], Patricio Yanez[21], Kynan Feeney[22], Michalis V. Karamouzis[23], Valerie Poulart[24], Ming Lei[24], Hong Xiao[24], Kaoru Kondo[24], Mingshun Li[24] & Yelena Y. Janjigian[25]✉

CheckMate 649: Overall Survival

PD-L1 CPS ≥5



All randomly assigned patients

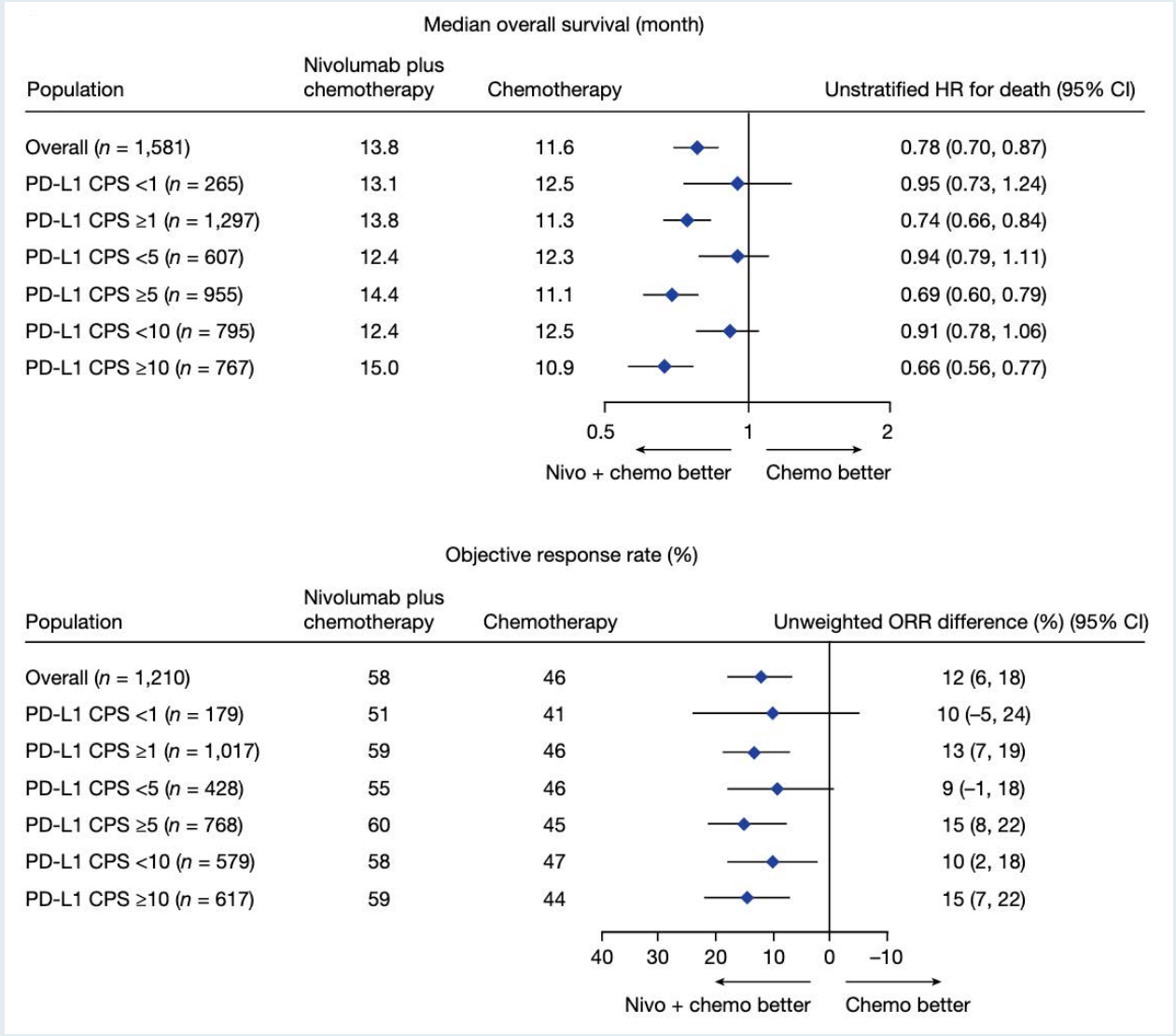


CPS = combined positive score

Shitara K et al. *Nature* 2022 March;603(7903):942-8.

RTP RESEARCH TO PRACTICE

CheckMate 649: Efficacy Subgroup Analysis by PD-L1 CPS Excluding Patients with Microsatellite Instability-High Tumors



Shitara K et al. *Nature* 2022 March;603(7903):942-8.

ESMO 2022 WORLD CONGRESS ON Gastrointestinal Cancer

O-3

Nivolumab plus chemotherapy or ipilimumab vs chemotherapy as first-line treatment for advanced esophageal squamous cell carcinoma: expanded efficacy and safety analyses from CheckMate 648

Ian Chau,[1] Jaffer A. Ajani,[2] Yuichiro Doki,[3] Jianming Xu,[4] Lucjan Wyrwicz,[5] Satoru Motoyama,[6] Takashi Ogata,[7] Hisato Kawakami,[8] Chih-Hung Hsu,[9] Antoine Adenis,[10] Farid El Hajbi,[11] Maria Di Bartolomeo,[12] Maria Ignez Braghiroli,[13] Eva Holtved,[14] Mariela Blum Murphy,[2] Sandzhar Abdullaev,[15] Samira Soleymani,[15] Ming Lei,[15] Ken Kato,[16] Yuko Kitagawa[17]

[1]Royal Marsden Hospital, London & Surrey, UK; [2]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Osaka University Graduate School of Medicine, Osaka, Japan; [4]Affiliated Hospital Cancer Center, Academy of Military Medical Sciences, Beijing, China; [5]Klinika Onkologii i Radioterapii, Narodowy Instytut Onkologii, Warszawa, Poland; [6]Akita University Hospital, Akita, Japan; [7]Kanagawa Cancer Center, Kanagawa, Japan; [8]Kindai University Faculty of Medicine, Osakasayama, Japan; [9]National Taiwan University Hospital, Taipei, Taiwan; [10]Institut du Cancer de Montpellier, Montpellier, France; [11]Centre Oscar Lambret, Lille, France; [12]Fondazione IRCCS Instituto Nazionale dei Tumori, Milan, Italy; [13]Institute of Cancer of São Paulo, University of São Paulo, São Paulo, Brazil; [14]Odense University Hospital, Odense, Denmark; [15]Bristol Myers Squibb, Princeton, NJ, USA; [16]National Cancer Center Hospital, Tokyo, Japan; [17]Keio University School of Medicine, Tokyo, Japan

CheckMate 648: Overall Survival by Baseline PD-L1 Status – Nivolumab with Chemotherapy versus Chemotherapy

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 645)		13.2	10.7	0.74	
Tumor cell PD-L1 expression[a]	< 1% (n = 329)	12.0	12.2	0.98	
	≥ 1% (n = 314)	15.4	9.2	0.55	
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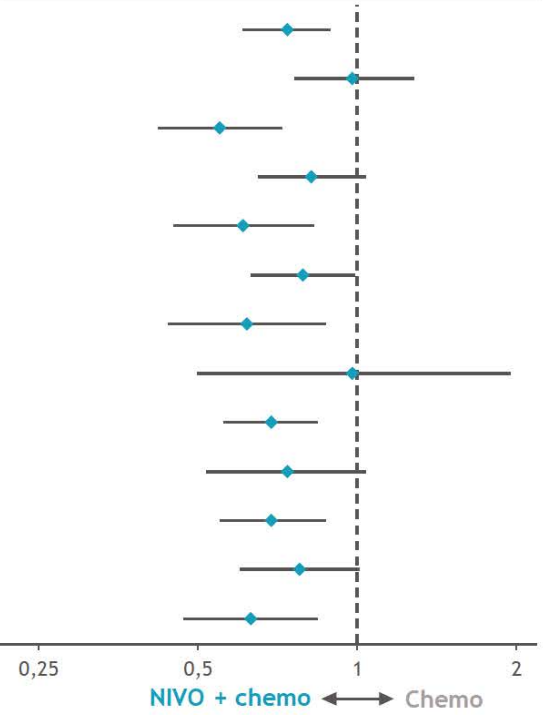
PD-L1 CPS[b,c]	< 1 (n = 51)	9.9	12.1	0.98	
	≥ 1 (n = 558)	13.8	9.8	0.69	
	< 5 (n = 188)	12.0	9.4	0.74	
	≥ 5 (n = 421)	15.2	11.1	0.69	
	< 10 (n = 329)	12.1	9.7	0.78	
	≥ 10 (n = 280)	16.1	11.6	0.63	



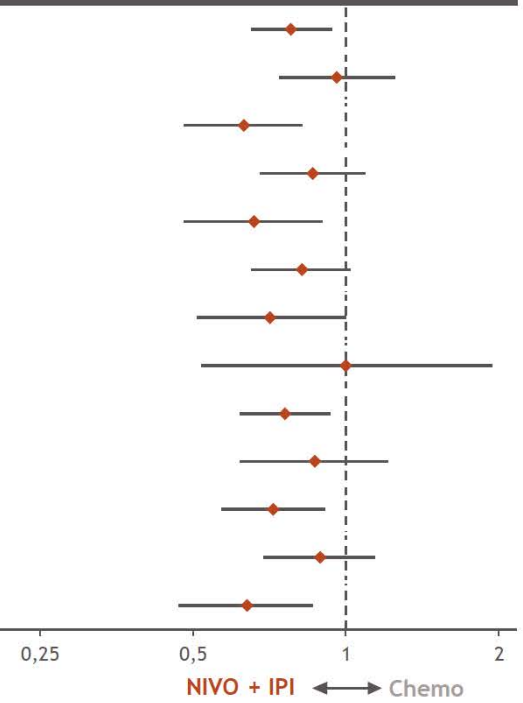
- HRs were below 1 favoring NIVO + chemo vs chemo across all PD-L1 expression subgroups
- Largest magnitude of benefit was observed in patients with tumor cell PD-L1 ≥ 1%, with no further enrichment in higher tumor cell PD-L1 expression subgroups

[a]Indeterminate, not evaluable, or missing (n = 2); [b]Indeterminate, not evaluable, or missing (n = 36); [c]Analysis by CPS was exploratory. Adapted from Doki Y, et al. *N Engl J Med* 2022;386:449-462.

Chau I et al. World Congress on Gastrointestinal Cancer 2022;Abstract O-3.

CheckMate 648: Overall Survival by Baseline PD-L1 Status – Nivolumab with Ipilimumab versus Chemotherapy Alone

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death	Unstratified HR (95% CI)
		NIVO + IPI	Chemo		
Overall (N = 649)		12.7	10.7	0.78	
Tumor cell PD-L1 expression[a]	< 1% (n = 330)	12.0	12.2	0.96	
	≥ 1% (n = 314)	13.7	9.2	0.63	
	< 5% (n = 409)	12.4	11.1	0.86	
	≥ 5% (n = 235)	13.0	9.5	0.66	
	< 10% (n = 444)	12.5	10.8	0.82	
	≥ 10% (n = 200)	13.0	9.5	0.71	
PD-L1 CPS[b,c]	< 1 (n = 55)	11.5	12.1	1.00	
	≥ 1 (n = 546)	12.7	9.8	0.76	
	< 5 (n = 197)	11.4	9.4	0.87	
	≥ 5 (n = 404)	14.5	11.1	0.72	
	< 10 (n = 330)	11.2	9.7	0.89	
	≥ 10 (n = 271)	16.7	11.6	0.64	



- HRs were below 1 favoring NIVO + IPI vs chemo across all PD-L1 expression subgroups, except for CPS < 1 (n = 55; HR = 1)
- Largest magnitude of benefit was observed in patients with tumor cell PD-L1 ≥ 1%, with no further enrichment in higher tumor cell PD-L1 expression subgroups

[a]Indeterminate, not evaluable, or missing (n = 5); [b]Indeterminate, not evaluable, or missing (n = 48); [c]Analysis by CPS was exploratory. Adapted from Doki Y, et al. *N Engl J Med* 2022;386:449-462.

Chau I et al. World Congress on Gastrointestinal Cancer 2022;Abstract O-3.

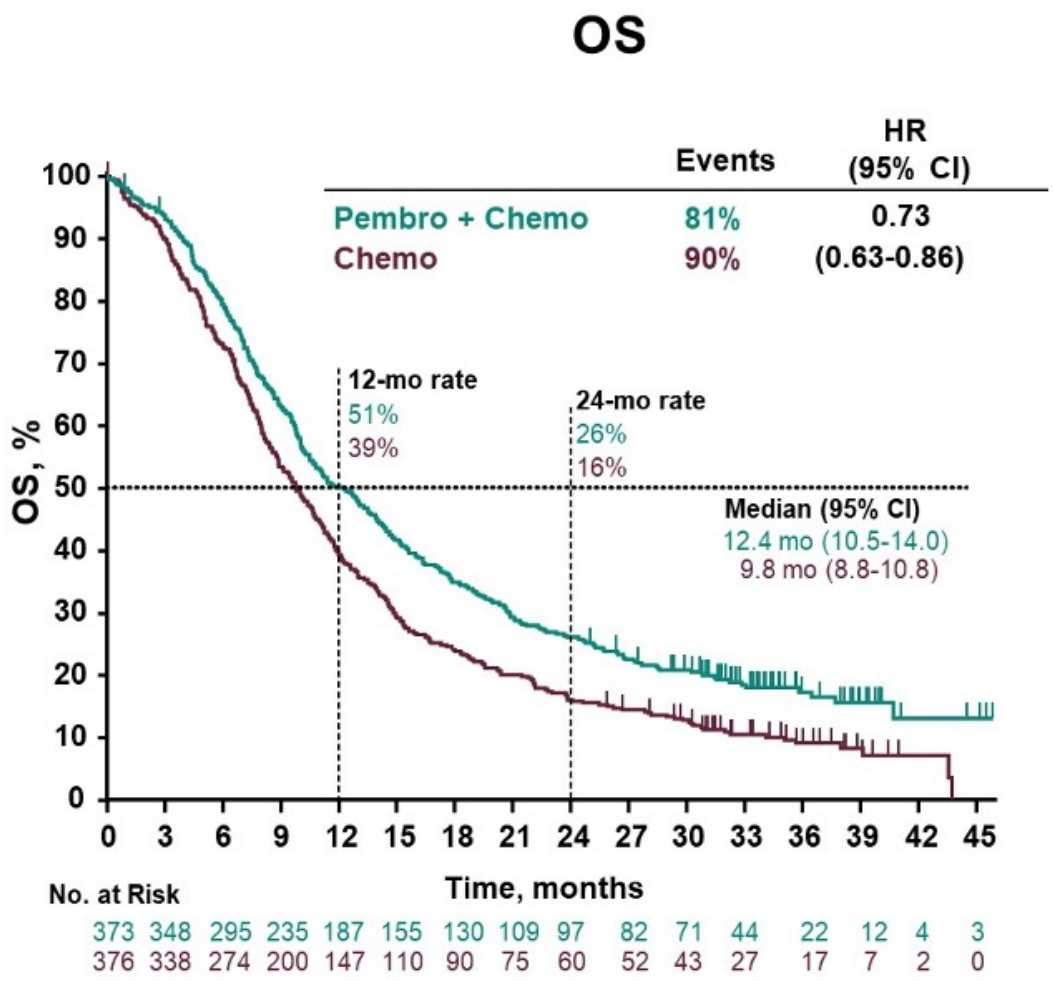
First-line Pembrolizumab Plus Chemotherapy Versus Chemotherapy in Advanced Esophageal Cancer: Longer-term Efficacy, Safety, and Quality-of-life Results From the Phase 3 KEYNOTE-590 Study

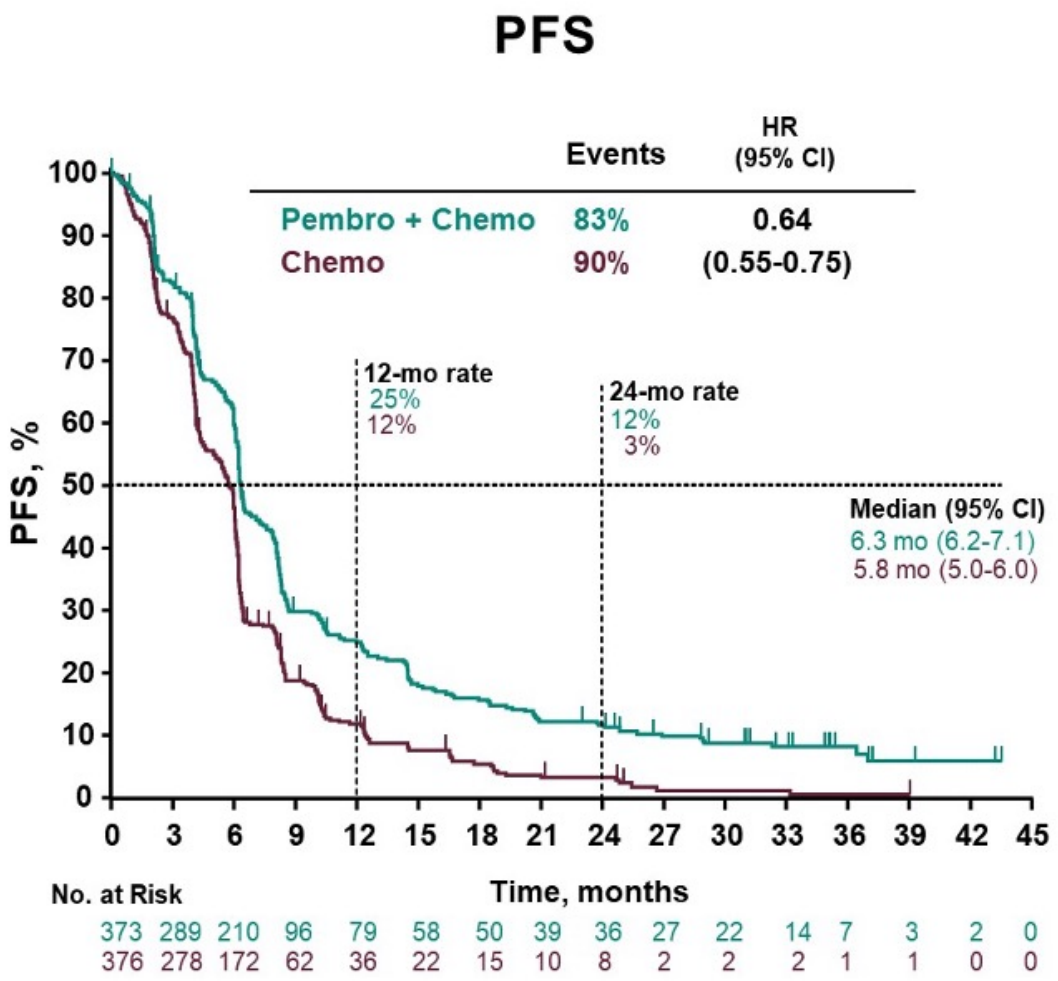
Jean-Philippe Metges,[1] Ken Kato,[2] Jong-Mu Sun,[3] Manish A. Shah,[4] Peter Enzinger,[5] Antoine Adenis,[6] Toshihiko Doi,[7] Takashi Kojima,[7] Zhigang Li,[8] Sung-Bae Kim,[9] Byoung Chul Cho,[10] Wasat Mansoor,[11] Shau-Hsuan Li,[12] Patrapim Sunpaweravong,[13] Maria Alsina Maqueda,[14] Gary L.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

[1]CHU Brest – Institut de Cancerologie et d'Hematologie ARPEGO Network, Brest, France; [2]National Cancer Center Hospital, Tokyo, Japan; [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [4]Weill Cornell Medical College, New York, NY, USA; [5]Dana Farber Cancer Institute, Boston, MA, USA; [6]IRCM, Inserm, Université Montpellier, ICM, Montpellier, France; [7]National Cancer Center Hospital East, Kashiwa, Japan; [8]Shanghai Chest Hospital Esophageal Disease Center, Shanghai, China; [9]Asan Medical Center, University of Ulsan College of Medicine, 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]Kaiser Permanente Southern California, Los Angeles Medical Center, Los Angeles, CA, USA; [16]Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; [17]Peking University Cancer Hospital & Institute; Beijing, China

Gastrointestinal Cancers Symposium 2022;Abstract 241

KEYNOTE-590: Survival Analyses (All Patients)



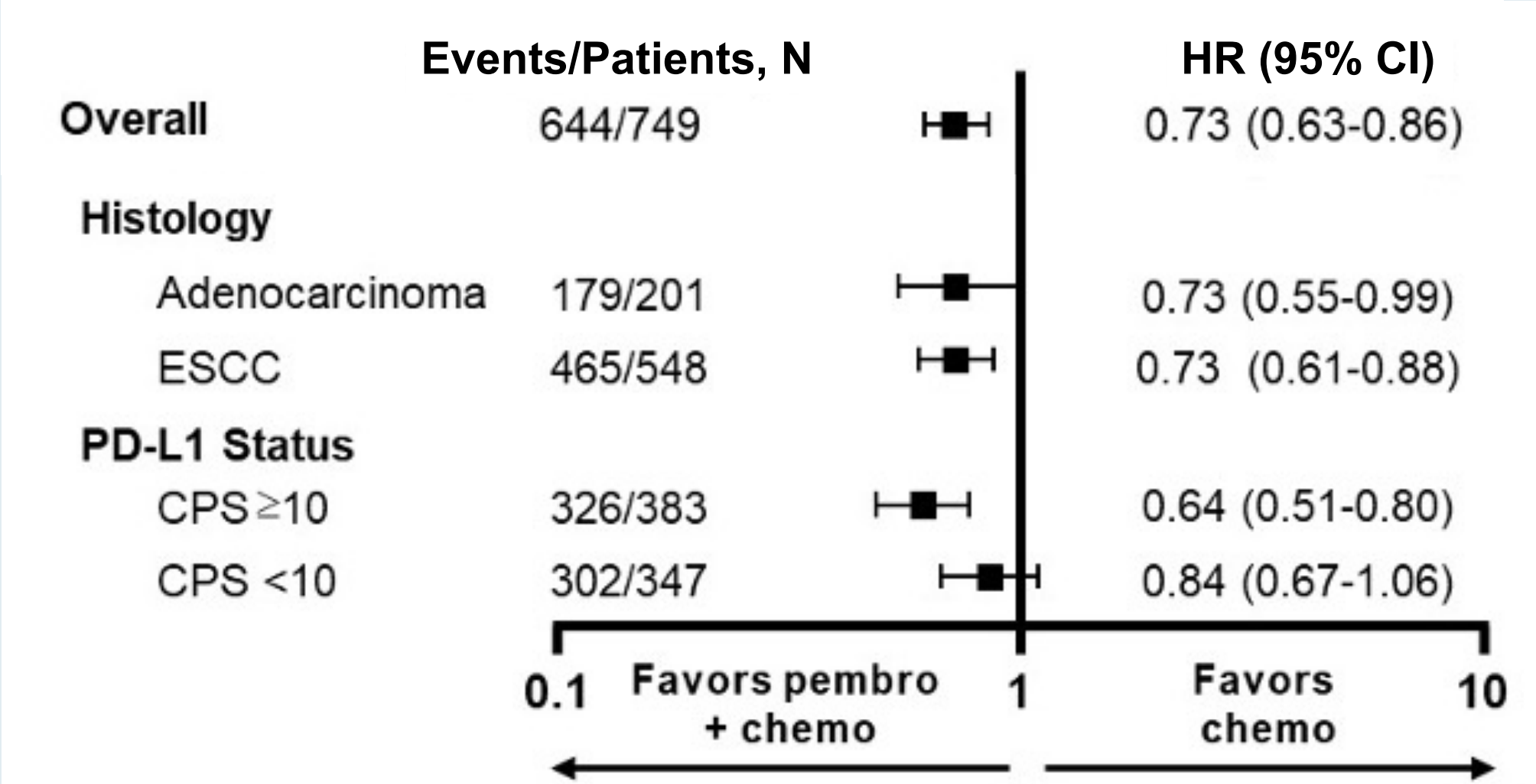


OS = overall survival; PFS = progression-free survival

Metges J-P et al. Gastrointestinal Cancers Symposium 2022;Abstract 241.

RTP RESEARCH TO PRACTICE

KEYNOTE-590: Overall Survival in Select Subgroups



ESCC = esophageal squamous cell carcinoma

Metges J-P et al. Gastrointestinal Cancers Symposium 2022;Abstract 241.

Nature 2021;600(7890):727-30.

Article

The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer

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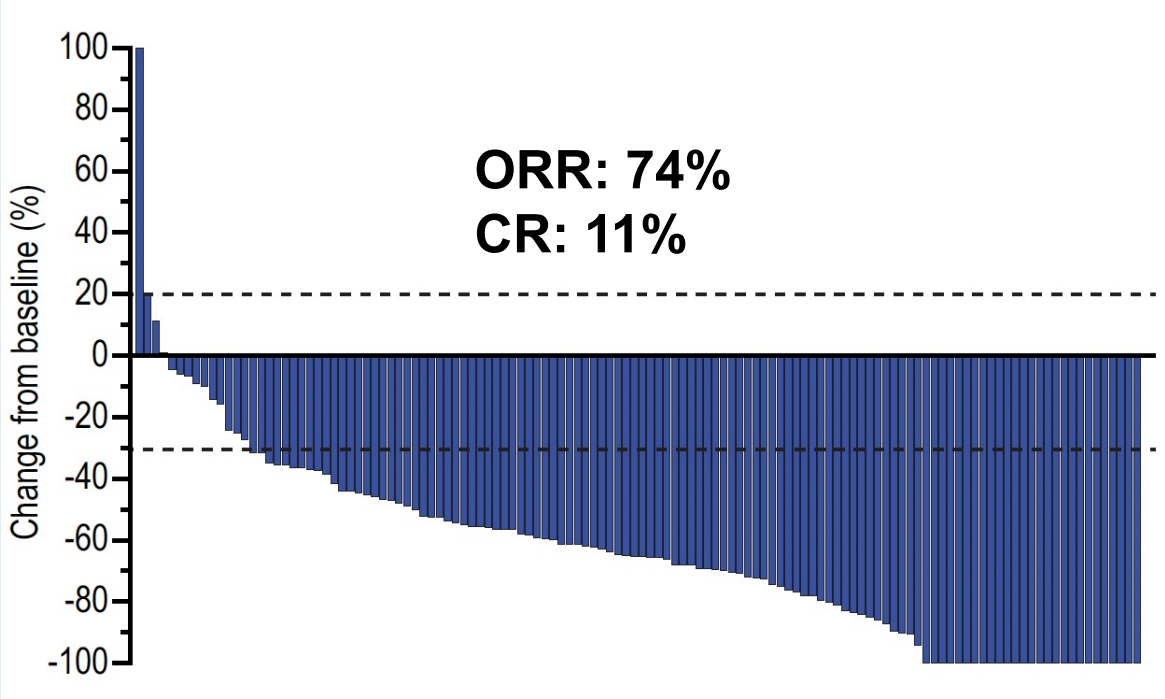
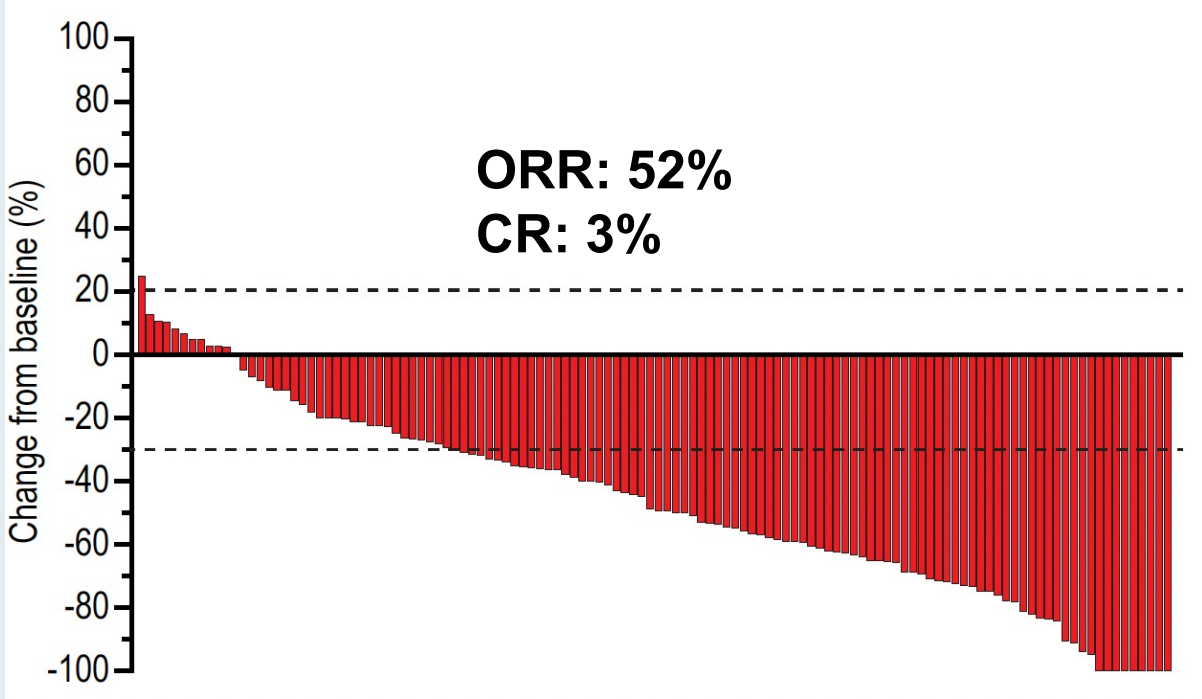
Yelena Y. Janjigian[1]✉, Akihito Kawazoe[2], Patricio Yañez[3], Ning Li[4], Sara Lonardi[5], Oleksii Kolesnik[6], Olga Barajas[7], Yuxian Bai[8], Lin Shen[9], Yong Tang[10], Lucjan S. Wyrwicz[11], Jianming Xu[12], Kohei Shitara[2], Shukui Qin[13], Eric Van Cutsem[14], Josep Tabernero[15], Lie Li[16], Sukrut Shah[16], Pooja Bhagia[16] & Hyun Cheol Chung[17]

KEYNOTE-811: Overall Response Rate (ORR)

Pembrolizumab/Trastuzumab/Chemotherapy



Placebo/Trastuzumab/Chemotherapy



Janjigian YY et al. *Nature* 2021;600(7890):727-30.

RTP RESEARCH TO PRACTICE

Poster 242

ASCO Gastrointestinal Cancers Symposium 2022

Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2–Positive Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma: Final Overall Survival (OS) Results From a Randomized, Multicenter, Open-Label, Phase 2 Study (DESTINY-Gastric01)

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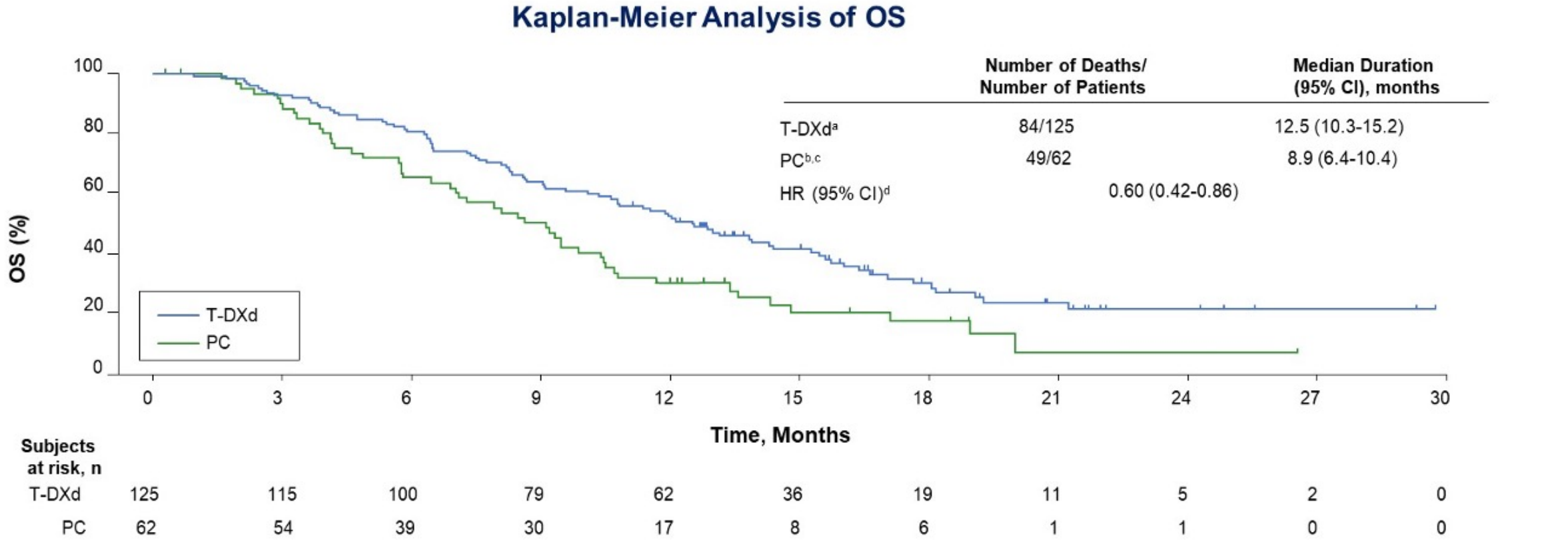
The Cancer Institute Hospital of JFCR, Tokyo, Japan

ON BEHALF OF THE DESTINY-GASTRIC01 INVESTIGATORS

Additional authors: Yung-Jue Bang, Satoru Iwasa, Naotoshi Sugimoto, Min-Hee Ryu, Daisuke Sakai, Hyun Cheol Chung, Hisato Kawakami, Hiroshi Yabusaki, Jeeyun Lee, Kaku Saito, Yoshinori Kawaguchi, Takahiro Kamio, Akihito Kojima, Masahiro Sugihara, Kohei Shitara

DESTINY-Gastric01: Final Overall Survival (OS)



PC = physician's choice

Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

PARIS 2022 ESMO congress

Updated Analysis of DESTINY-Gastric02: a Phase 2 Single-Arm Trial of Trastuzumab Deruxtecan (T-DXd) in Western Patients with HER2-Positive Unresectable/Metastatic Gastric/Gastroesophageal Junction (GEJ) Cancer Who Progressed on or After Trastuzumab-Containing Regimen

Presentation 1205MO

Geoffrey Ku,[a] Maria di Bartolomeo, Elizabeth Smyth, Ian Chau, Haeseong Park, Salvatore Siena, Sara Lonardi, Zev A. Wainberg, Jaffer Ajani, Joseph Chao, Ferdous Barlaskar, Yoshinori Kawaguchi, Amy Qin, Jasmeet Singh, Aashima Puri, Gerold Meinhardt, Eric Van Cutsem

On behalf of the DESTINY-Gastric02 investigators

[a]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Paris, France, September 9-13, 2022

DESTINY-Gastric02 Primary Endpoint: Objective Response Rate (ORR)

Response Assessment by ICR	April 9, 2021 Data Cutoff[a] Patients (N = 79)	November 8, 2021 Data Cutoff[b] Patients (N = 79)
Confirmed ORR,[c] % (n)	**38.0** (30) (95% CI, 27.3-49.6)	**41.8** (33) (95% CI, 30.8-53.4)
Confirmed best overall response, % (n)		
CR	**3.8** (3)	**5.1** (4)
PR	**34.2** (27)	**36.7** (29)
SD	**43.0** (34)	**39.2** (31)
PD	**16.5** (13)	**16.5** (13)
Not evaluable	**2.5** (2)	**2.5** (2)
Confirmed DCR,[d] % (n)	**81.0** (64) (95% CI, 70.6-89.0)	**81.0** (64) (95% CI, 70.6-89.0)
Median DoR, months	8.1 (95% CI, 4.1-NE)	8.1 (95% CI, 5.9-NE)[e]
Median TTR, months	1.4 (95% CI, 1.4-2.6)	1.4 (95% CI, 1.4-2.7)

Median PFS	**5.6 mo**
Median OS	**12.1 mo**

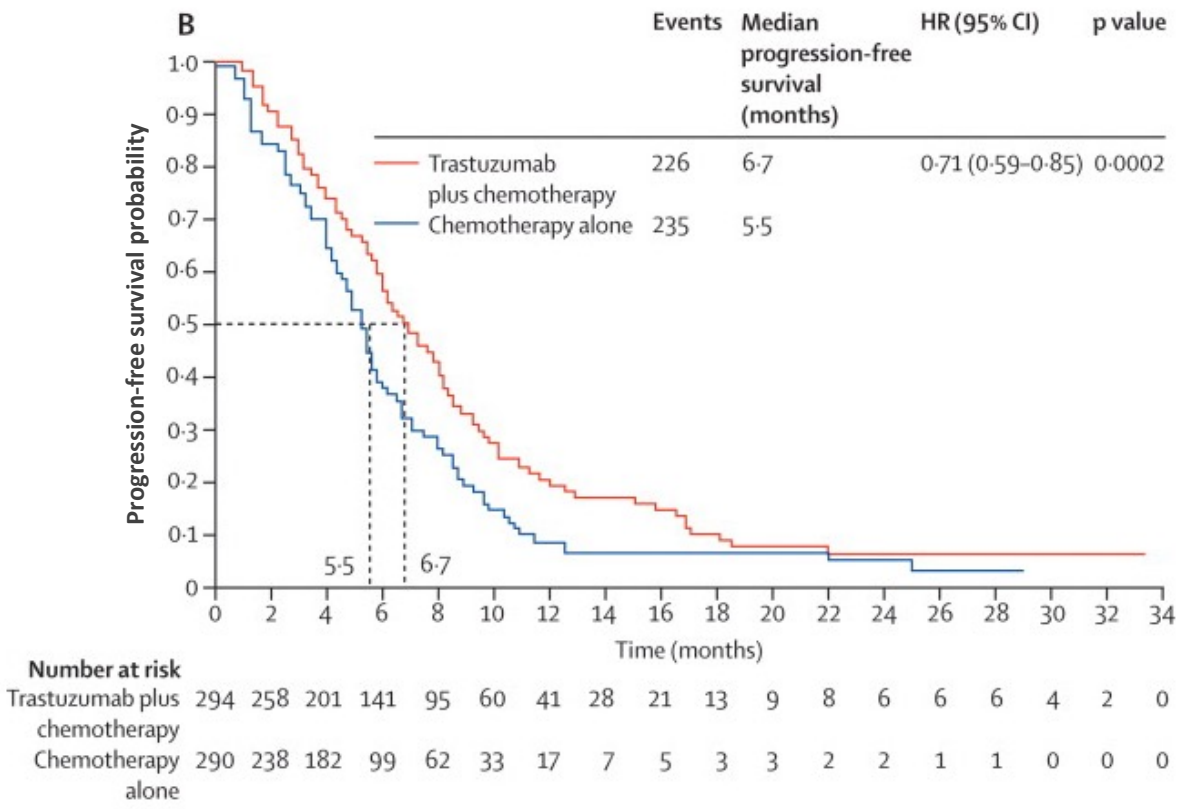
Ku G et al. ESMO 2022;Abstract 1205MO.

HER2 AS AN ACTIONABLE TARGET IN GI CANCERS

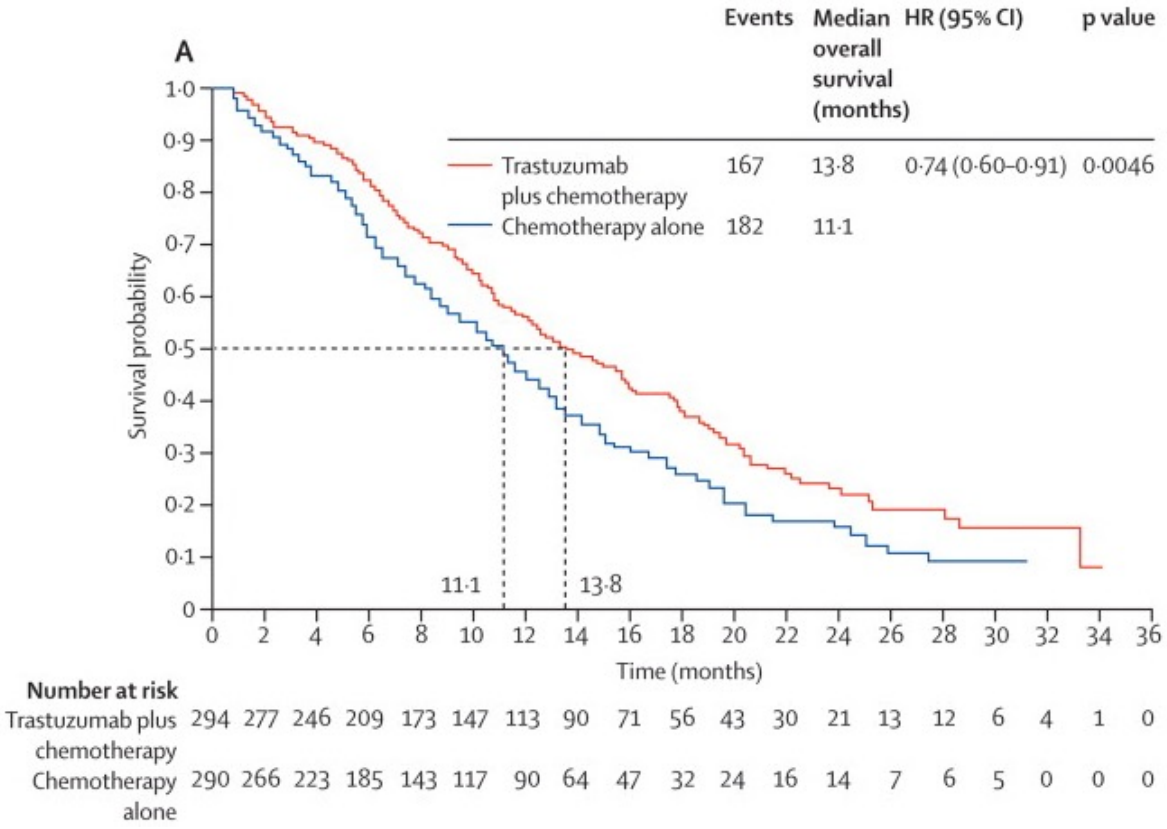
John Strickler, MD
Duke University
October 22, 2022

1L Trastuzumab improves survival for patients with metastatic HER2+ gastric/GEJ adenoca

Progression-free survival



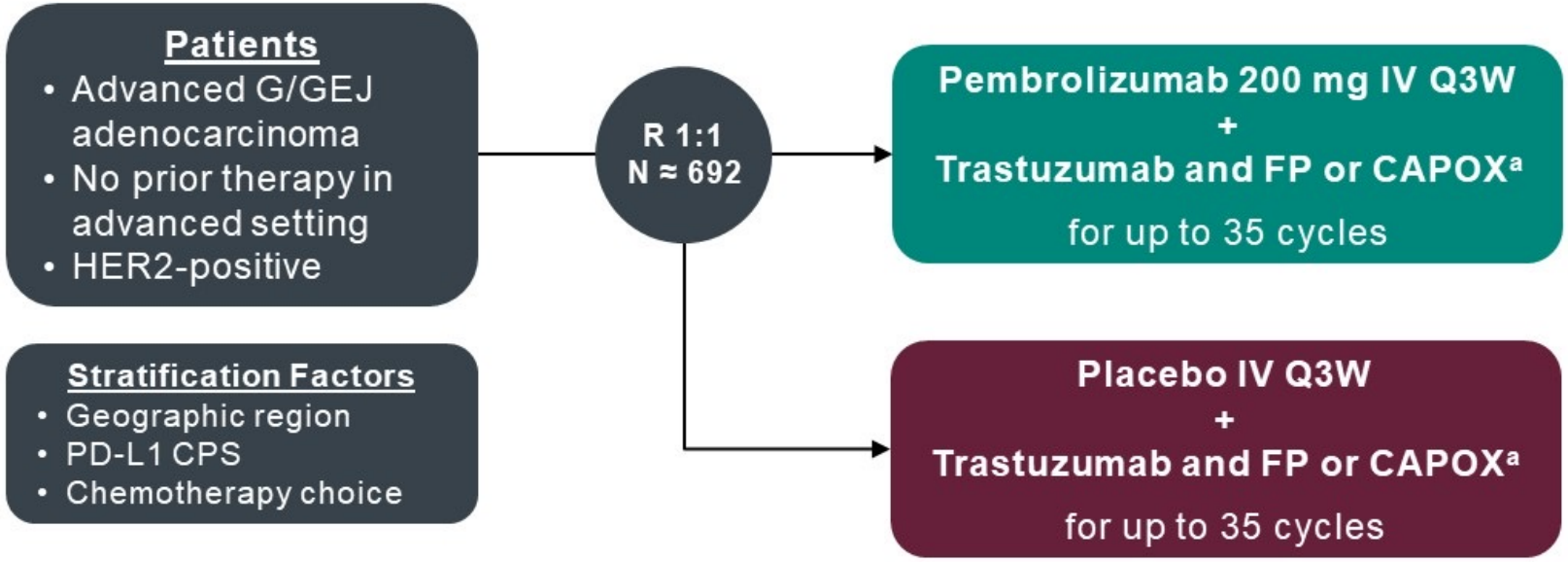
Overall survival



Overall survival for IHC3+ or IHC2+/FISH+: 16.0 vs 11.8 months (HR=0.65; 0.51-0.83)

Bang et al., *Lancet* 2010; 376: 687-97

KEYNOTE-811: Chemo + trastuzumab +/- pembrolizumab



Dual Primary End Points
- OS
- PFS (RECIST v1.1 per BICR)

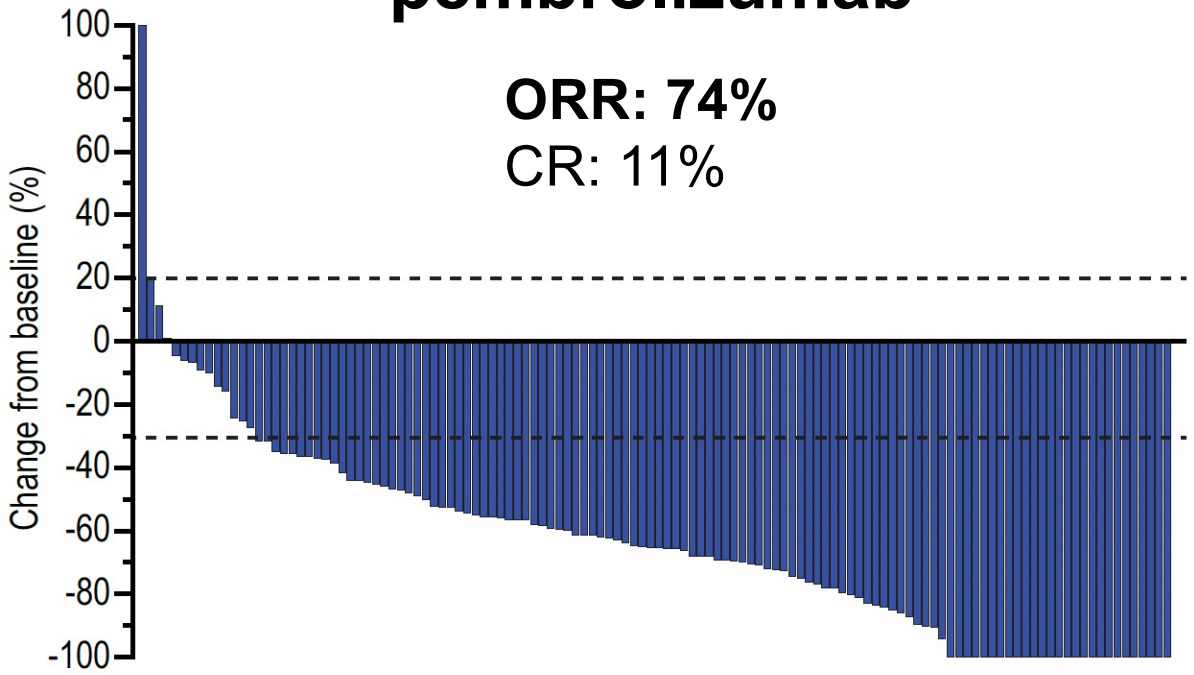
Secondary End Points
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

Janjigian et al., Presented at 2021 ASCO Annual Meeting

KEYNOTE-811: Overall response rate favors pembrolizumab

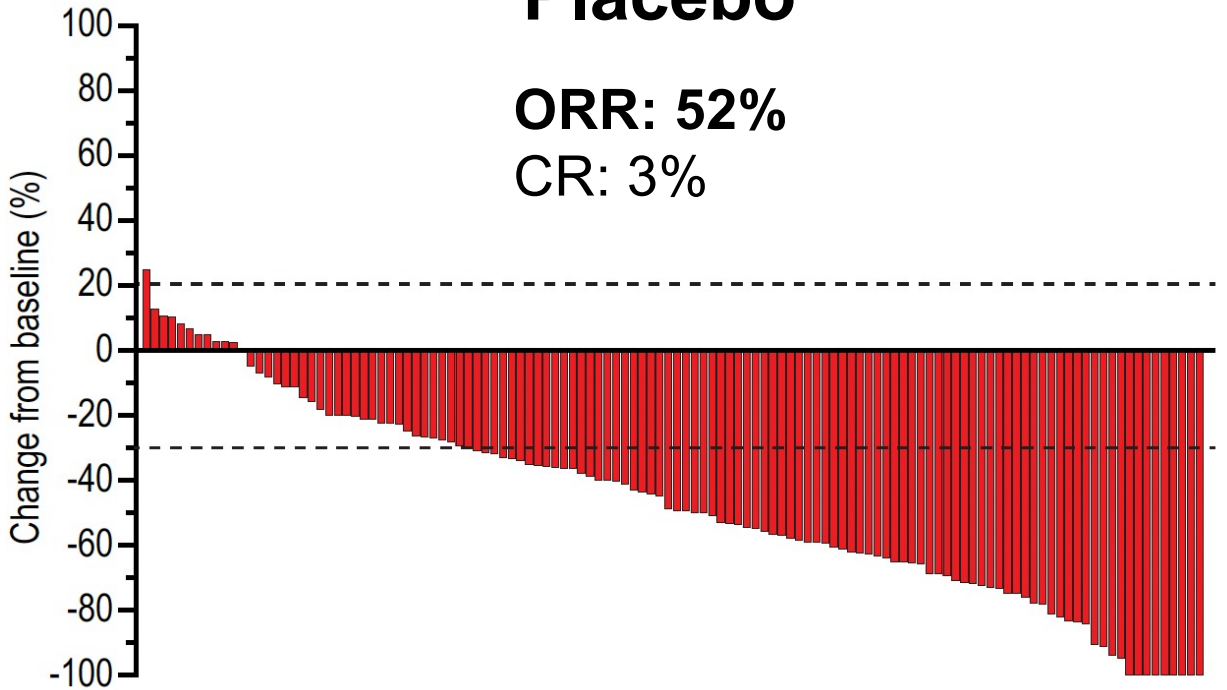
Chemo + trastuzumab + pembrolizumab

ORR: 74%
CR: 11%



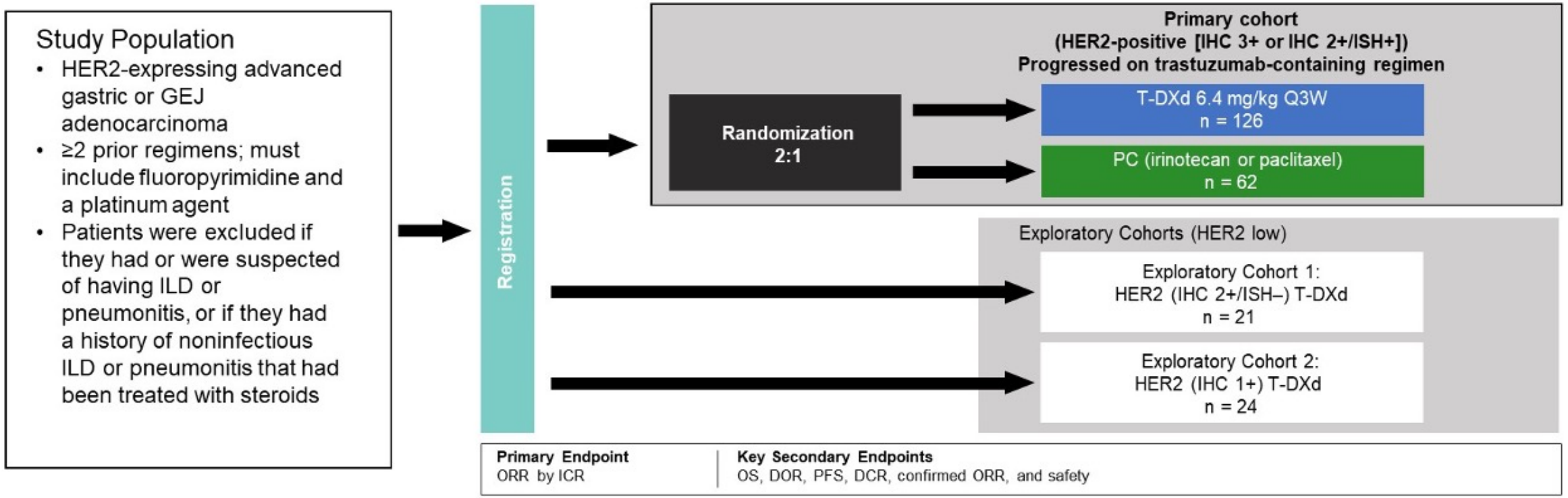
Chemo + trastuzumab + Placebo

ORR: 52%
CR: 3%



Janjigian YY et al. *Nature* 2021;600(7890):727-30.

DESTINY-Gastric01 Randomized, Phase II Study Design

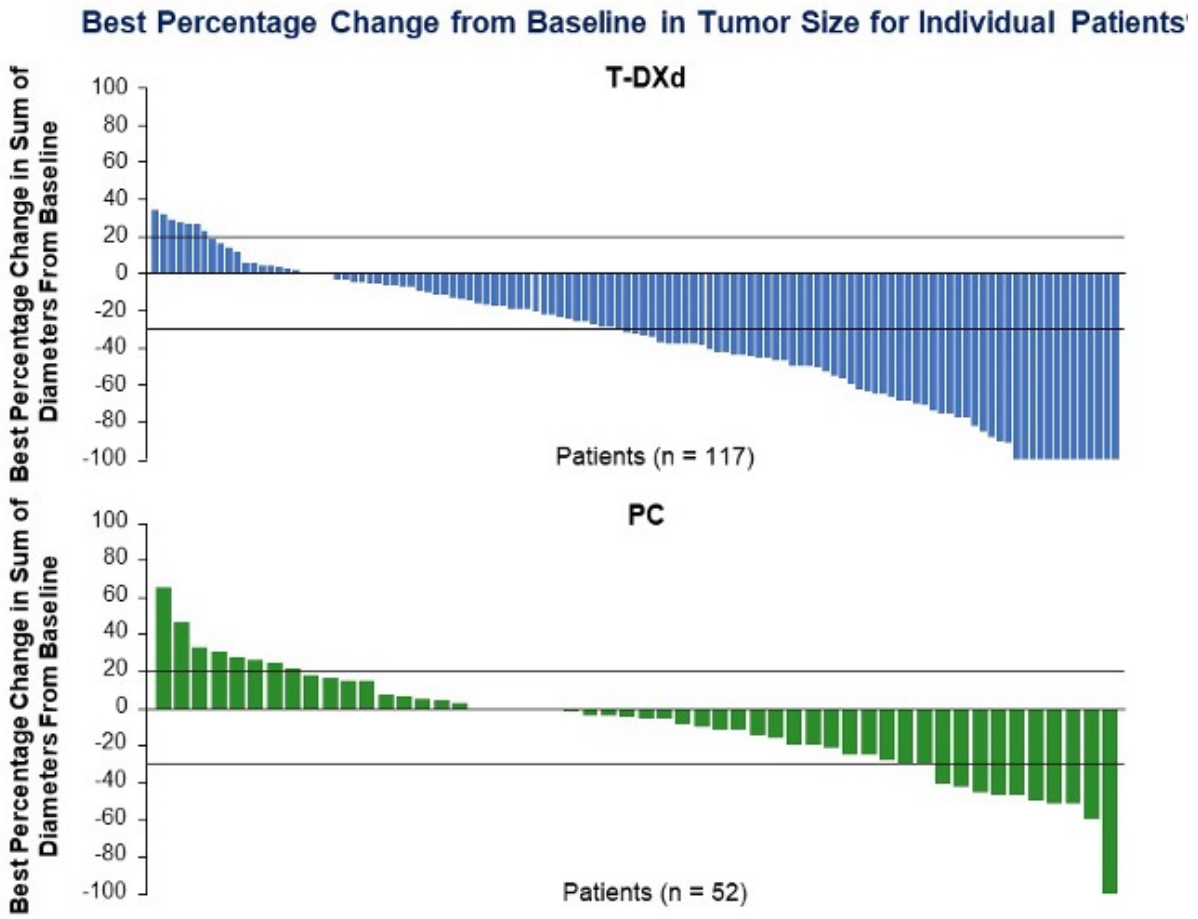


PC = physician's choice

Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

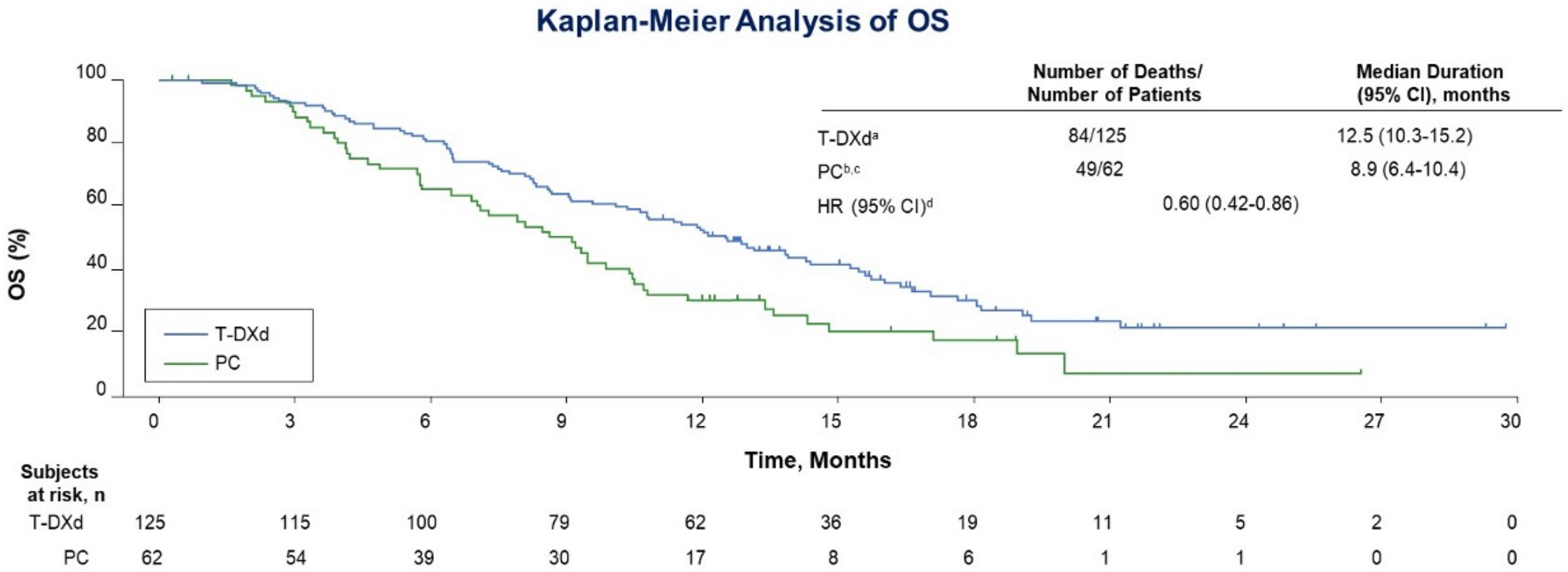
DESTINY-Gastric01: Antitumor Activity

	T-DXd n = 119	PC Overall n = 56
ORR (CR + PR) by ICR, n (%)[a]	**61 (51.3) 95% CI, 41.9-60.5**	**8 (14.3) 95% CI, 6.4-26.2**
	P < 0.0001[b]	
CR	11 (9.2)	0
PR	50 (42.0)	8 (14.3)
SD	42 (35.3)	27 (48.2)
PD	14 (11.8)	17 (30.4)
Not evaluable	2 (1.7)	4 (7.1)
Confirmed ORR (CR + PR) by ICR, n (%)[a]	50 (42.0) 95% CI, 33.0-51.4	7 (12.5) 95% CI, 5.2-24.1
CR	10 (8.4)	0
PR	40[c] (33.6)	7 (12.5)
SD	52 (43.7)	28 (50.0)
PD	14 (11.8)	17 (30.4)
Not evaluable	3 (2.5)	4 (7.1)
Confirmed DCR (CR + PR + SD), n (%)[a]	102 (85.7) 95% CI, 78.1-91.5	35 (62.5) 95% CI, 48.5-75.1
Confirmed DOR, median, months	12.5 95% CI, 5.6-NE	3.9 95% CI, 3.0-4.9
TTR, median, months	1.5 95% CI, 1.4-1.7	1.6 95% CI, 1.3-1.7



Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

DESTINY-Gastric01: Final Overall Survival (OS)



Yamaguchi K et al. Gastrointestinal Cancers Symposium 2022;Abstract 242.

PARIS 2022 ESMO congress

Updated Analysis of DESTINY-Gastric02: a Phase 2 Single-Arm Trial of Trastuzumab Deruxtecan (T-DXd) in Western Patients with HER2-Positive Unresectable/Metastatic Gastric/Gastroesophageal Junction (GEJ) Cancer Who Progressed on or After Trastuzumab-Containing Regimen

Presentation 1205MO

Geoffrey Ku,[a] Maria di Bartolomeo, Elizabeth Smyth, Ian Chau, Haeseong Park, Salvatore Siena, Sara Lonardi, Zev A. Wainberg, Jaffer Ajani, Joseph Chao, Ferdous Barlaskar, Yoshinori Kawaguchi, Amy Qin, Jasmeet Singh, Aashima Puri, Gerold Meinhardt, Eric Van Cutsem

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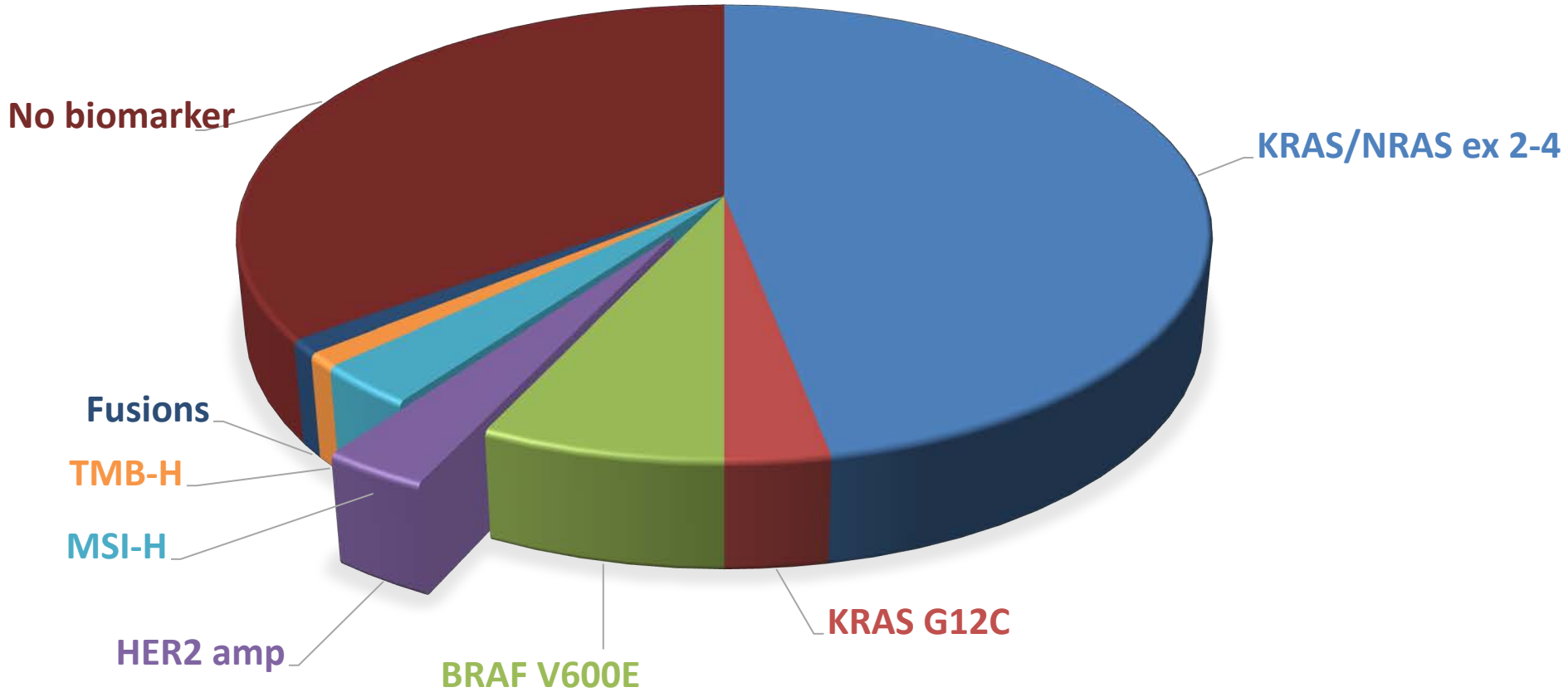
Confirmed best overall response, % (n)		
CR	**3.8** (3)	**5.1** (4)
PR	**34.2** (27)	**36.7** (29)
SD	**43.0** (34)	**39.2** (31)
PD	**16.5** (13)	**16.5** (13)
Not evaluable	**2.5** (2)	**2.5** (2)
Confirmed DCR,[d] % (n)	**81.0** (64) (95% CI, 70.6-89.0)	**81.0** (64) (95% CI, 70.6-89.0)
Median DoR, months	8.1 (95% CI, 4.1-NE)	8.1 (95% CI, 5.9-NE)[e]
Median TTR, months	1.4 (95% CI, 1.4-2.6)	1.4 (95% CI, 1.4-2.7)

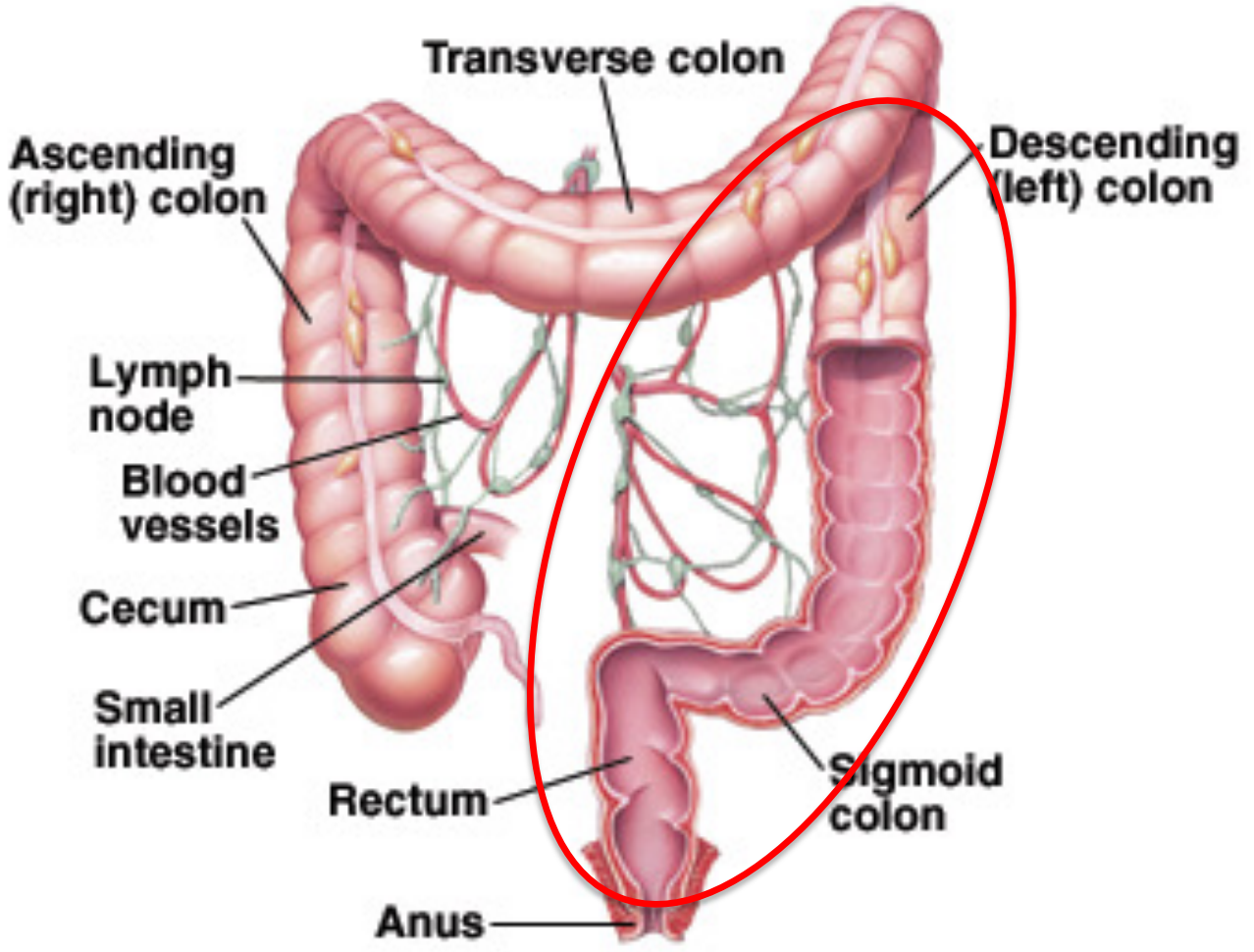
Median OS at November 8, 2021 data cutoff = 12.1 mo; median PFS = 5.6 mo

Actionable colorectal cancer targets in 2022



HER2 in Metastatic CRC

- Usually left sided
- Distinctive pattern of metastatic disease
- Not mutually exclusive with *RAS* or *BRAF* mutations
- Not associated with worse prognosis
- Associated with EGFR resistance



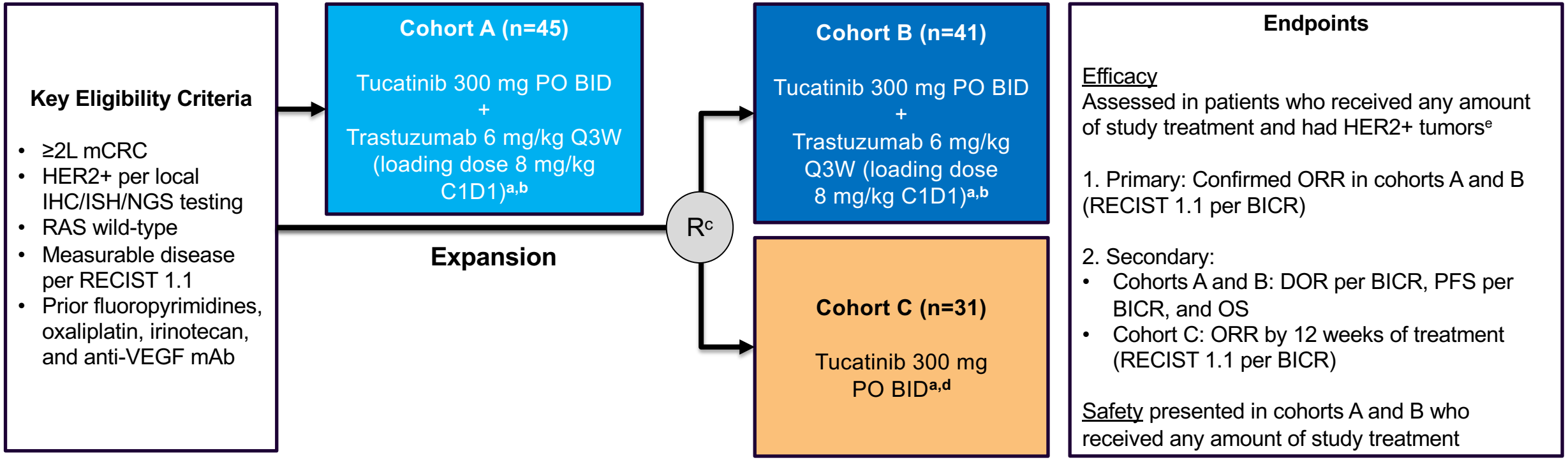
Results of dual anti-HER2 clinical trials in patients with treatment refractory HER2+ metastatic CRC

Clinical trial	Therapies	Patients (N)	Response Rate	PFS (median)
HERACLES	Lapatinib + Trastuzumab	27	28% (Inv)	4.7 months
MyPathway	Pertuzumab + Trastuzumab	68 (RAS WT)	31% (Inv)	5.3 months*
MOUNTAINEER	Tucatinib + Trastuzumab	84	38% (ICR)	8.2 months

* Based on first 43 patients treated, not updated

Sartore-Bianchi et al., *Lancet Oncology* 2016 17, 738-746.
Meric-Bernstam et al., *Lancet Oncol* Vol20, Issue 4, April 2019, 518-530.
Meric-Bernstam et al., J Clin Oncol 39, 2021 (suppl 15; abstr 3004)
Strickler et al., ESMO World GI 2022 - presentation

MOUNTAINEER: Global, Open-Label Phase II Trial



MOUNTAINEER began as a US investigator-sponsored trial and initially consisted of a single cohort (cohort A) and was expanded globally to include patients randomly assigned to receive tucatinib + trastuzumab (cohort B) or tucatinib monotherapy (cohort C)

Data cut-off for current analysis, March 28, 2022

a. Each treatment cycle is 21 days; b. Patients remained on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure; c. Stratification: Left sided tumor primary vs other; d. Patients were allowed to cross over and receive tucatinib and trastuzumab if they experienced radiographic progression at any time point or if they had not achieved a PR or CR by week 12; e. Patients had HER2+ tumors as defined by one or more protocol required local tests: IHC 3+ (n=46), amplification by ISH (n=36), or amplification by NGS (n=69)

2L+, second line and later; BICR, blinded independent central review; BID, twice a day; C1D1, cycle 1 day 1; CR, complete response; DOR, duration of response; HER2, human epidermal growth receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; PR, partial response; R, randomisation; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; US, United States; VEGF, vascular endothelial growth factor.

https://clinicaltrials.gov/ct2/show/NCT03043313

Strickler JH et al. ESMO GI 2022;Abstract LBA2.

Tucatinib + Trastuzumab: Efficacy Outcomes

Responses	Tucatinib + Trastuzumab Cohorts A+B n=84
Best overall response per BICR[a], n (%)	
CR	3 (3.6)
PR	29 (34.5)
SD[b]	28 (33.3)
PD	22 (26.2)
Not available[c]	2 (2.4)
cORR per BICR, % (95% CI)[d]	**38.1 (27.7, 49.3)**
cORR per Investigator, % (95% CI)[d]	42.9 (32.1, 54.1)
Median time to objective response per BICR[e], months (range)	2.1 (1.2, 9.8)
DCR[f] per BICR, n (%)	60 (71.4)
Median DOR per BICR, months (95% CI)	**12.4 (8.5, 20.5)**

a. Confirmed best overall response assessed per RECIST 1.1; b. Includes SD and non-CR/non-PD; c. Includes patients with no post-baseline response assessment and patients whose disease assessments are not evaluable; d. Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934); e. Time from the start of study treatment (Cohort A) or date of randomisation (Cohort B) to the first documentation of objective response (CR or PR that is subsequently confirmed); f. Defined as sum of CR, PR, and SD

BICR, blinded independent central review; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

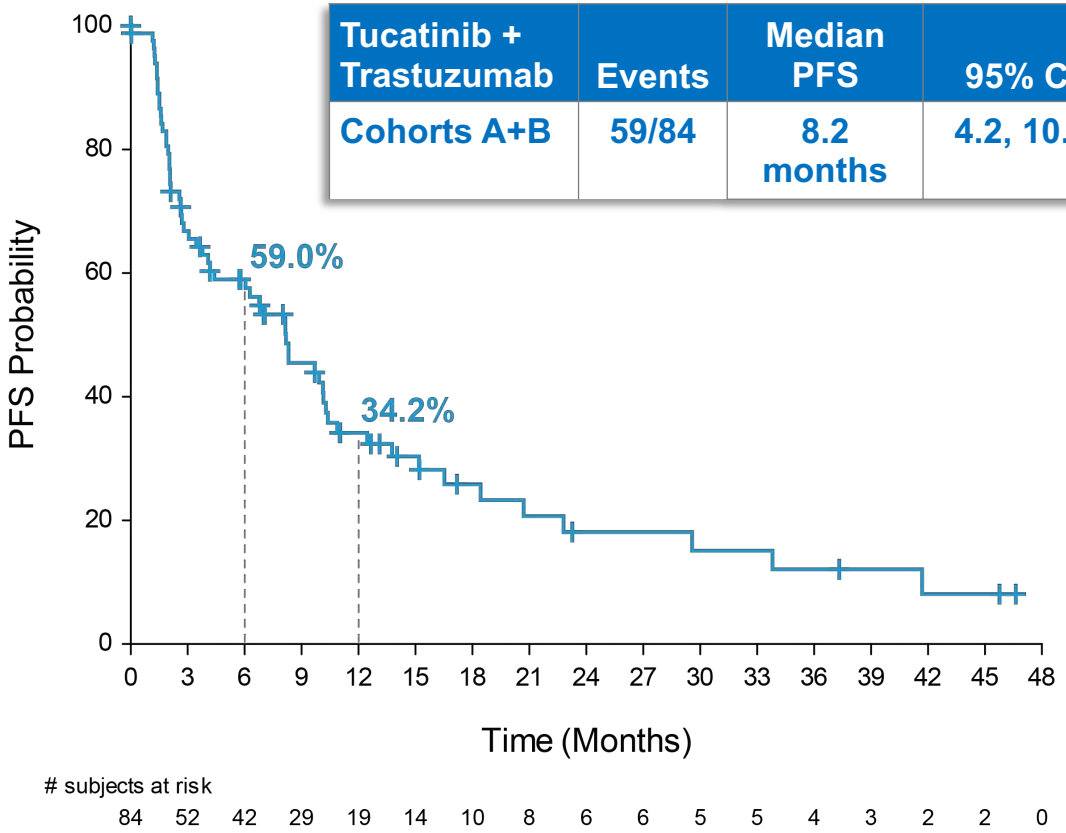
Data cutoff: 28 Mar 2022

Strickler JH et al. ESMO GI 2022;Abstract LBA2.

Tucatinib + Trastuzumab: PFS and OS

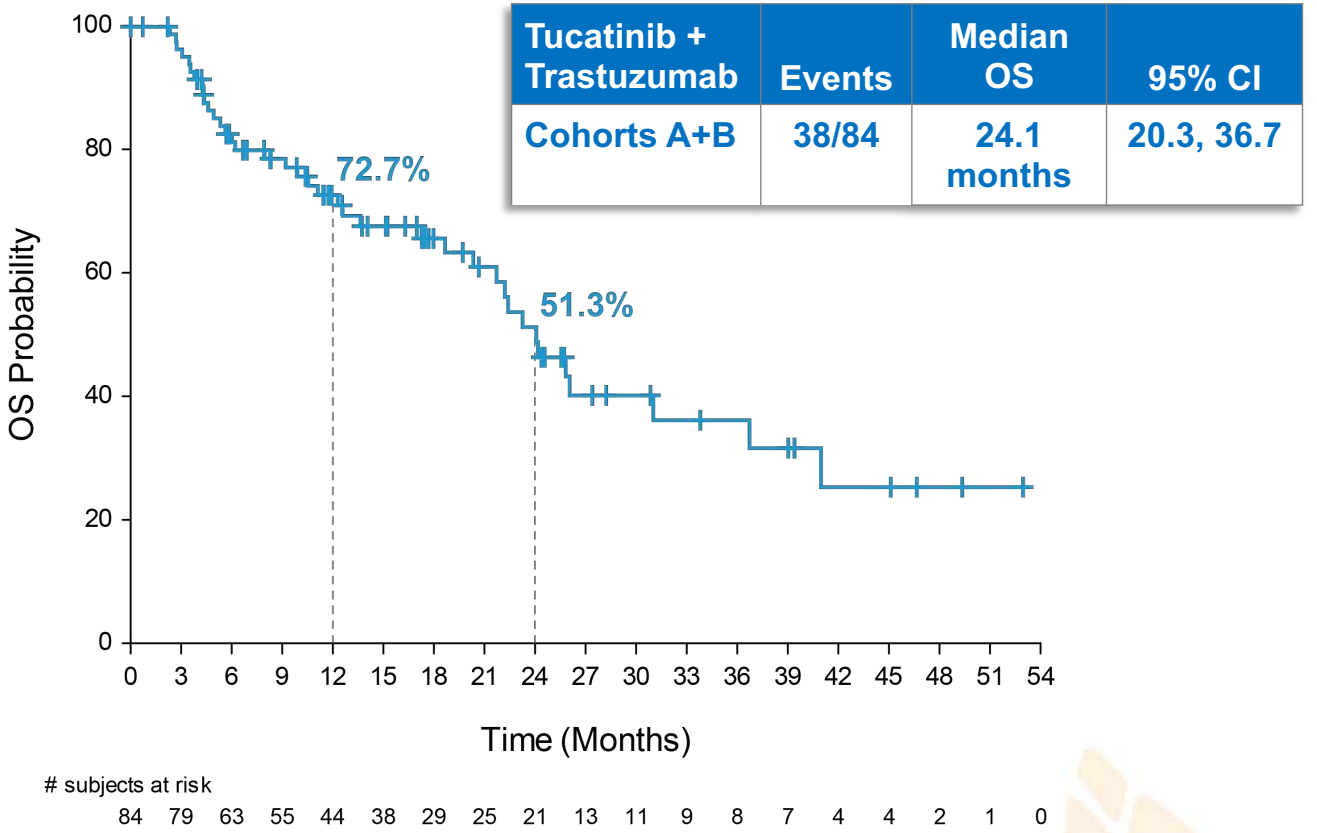
Progression-Free Survival per BICR

Tucatinib + Trastuzumab	Events	Median PFS	95% CI
Cohorts A+B	59/84	8.2 months	4.2, 10.3



Overall Survival

Tucatinib + Trastuzumab	Events	Median OS	95% CI
Cohorts A+B	38/84	24.1 months	20.3, 36.7



Median follow-up for Cohorts A+B was 20.7 months (IQR, 11.7, 39.0)

BICR, blinded independent central review; IQR, interquartile range; OS, overall survival; PFS, progressive-free survival.

Data cutoff: 28 Mar 2022

Strickler JH et al. ESMO GI 2022;Abstract LBA2.

Adverse Events of Special Interest with Tucatinib + Trastuzumab

- Diarrhea
  - Most common TEAE: Grade 1, 50.0%; Grade 2, 10.5%; Grade 3, 3.5%
    - No treatment discontinuations due to diarrhea
    - Tucatinib dose modifications for diarrhea: dose reduction, 2.3%; dose hold, 3.5%
  - Antidiarrheal prophylaxis was not mandated

- Hepatotoxicity
  - Grade ≥3: increased ALT (3.5%), increased AST (2.3%), and hypertransaminasemia (1.2%)
  - Hepatotoxicity leading to tucatinib modification or discontinuation occurred in 5.8%
  - No Hy's law cases identified

- Cardiotoxicity
  - Asymptomatic LVEF decrease leading to dose modification or discontinuation occurred in 3.5%

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LVEF, left ventricular ejection fraction; TEAE, treatment-emergent adverse event.
Data cutoff: 28 Mar 2022

Strickler JH et al. ESMO GI 2022;Abstract LBA2.

DESTINY-CRC-01: Trastuzumab deruxtecan (T-DXd; ds8201a) for HER2+ mCRC - Phase 2 study design

Key Eligibility Criteria (n=86)[2]

≥2L+ mCRC

HER2+ per **central confirmation**

RAS/BRAF wild type Prior anti-HER2 allowed

All patients received trastuzumab deruxtecan 6.4mg/kg IV Q3 weeks

NCT03384940

Cohort A
HER2 Positive – IHC3+ or IHC2+/ISH+ (n=53)

ORR= 45%
PFS= 6.9 m

Cohort B
HER2 IHC2+/ISH- (n=15)[2]

ORR= 0% [2]
PFS= 2.1m

Cohort C
HER2 IHC 1+ (n=18)

ORR= 0% [2]
PFS= 1.4m

At data cutoff (Dec 28, 2020)

Primary Endpoint:

- Confirmed ORR (RECIST v1.1 by BICR)

Secondary Endpoints:

- DOR
- DCR
- PFS
- OS
- ORR in cohorts B and C (RECIST 1.1 by BICR)

- T-DXd is an antibody drug conjugate with a humanized anti-HER2 IgG1 mAb similar to trastuzumab[1]
- Topoisomerase I inhibitor payload[1]
- High payload-to-antibody ratio (8:1)[3]

BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; HER2+, HER2 gene amplification; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

1. Siena et al., Lancet Oncol 2021; 2. Yoshino T et al., JCO.2021; 3. Nakada T et al., Chem Pharm Bull (Tokyo). 2019

DESTINY-CRC-01: Trastuzumab deruxtecan for HER2+ mCRC - Most common TEAEs (≥10%)

(All cohorts, N=78)

	Grade 1-2	Grade 3	Grade 4	Grade 5
Nausea	42 (54%)	5 (6%)	0	0
Decreased appetite	26 (33%)	0	0	0
Fatigue	25 (32%)	1 (1%)	0	0
Vomiting	22 (28%)	1 (1%)	0	0
Diarrhoea	21 (27%)	1 (1%)	0	0
Anaemia	18 (23%)	10 (13%)	1 (1%)	0
Platelet count decreased	16 (21%)	5 (6%)	2 (3%)	0
Alopecia	15 (19%)	0	0	0
Constipation	11 (14%)	0	0	0
Asthenia	10 (13%)	0	0	0
Neutrophil count decreased	9 (12%)	12 (15%)	5 (6%)	0
Cough	9 (12%)	0	0	0
Oedema peripheral	9 /12%)	0	0	0
Pyrexia	9 (12%)	0	0	0
Hypokalaemia	8 (10%)	4 (5%)	1 (1%)	0

- Five (6%) of 78 patients had interstitial lung disease or pneumonitis
  - Grade 2 = 2 patients
  - Grade 3 = 1 patient
  - Grade 5 = 2 patients
- Median time to onset date of interstitial lung disease or pneumonitis was 77 days
- 2 recovered, 1 did not recover and died of disease progression, and 2 died due to the AE

AE, adverse event; HER2+, HER2 gene amplification; mCRC, metastatic colorectal cancer; TEAE, treatment-emergent adverse event.

Siena et al., Lancet Oncol 2021.

HER2 in GI cancers: Final thoughts

- For HER2+ metastatic gastric/ GEJ adenoca
  - 1L SOC: FOLFOX+trastuzumab+pembro
  - 2nd/3rd line: Trastuzumab deruxtecan (consider repeat biopsy to confirm HER2+)

- For RAS wild-type HER2+ metastatic CRC
  - *HER2* amp associated with resistance to anti-EGFR therapies
  - Lapatinib + trastuzumab, pertuzumab + trastuzumab, and trastuzumab deruxtecan in NCCN guidelines after 1L chemotherapy
  - Tucatinib + trastuzumab has high ORR and DoR with favorable tolerability – may become a new SOC option
  - Trastuzumab deruxtecan retains activity after progression on prior anti-HER2 therapies

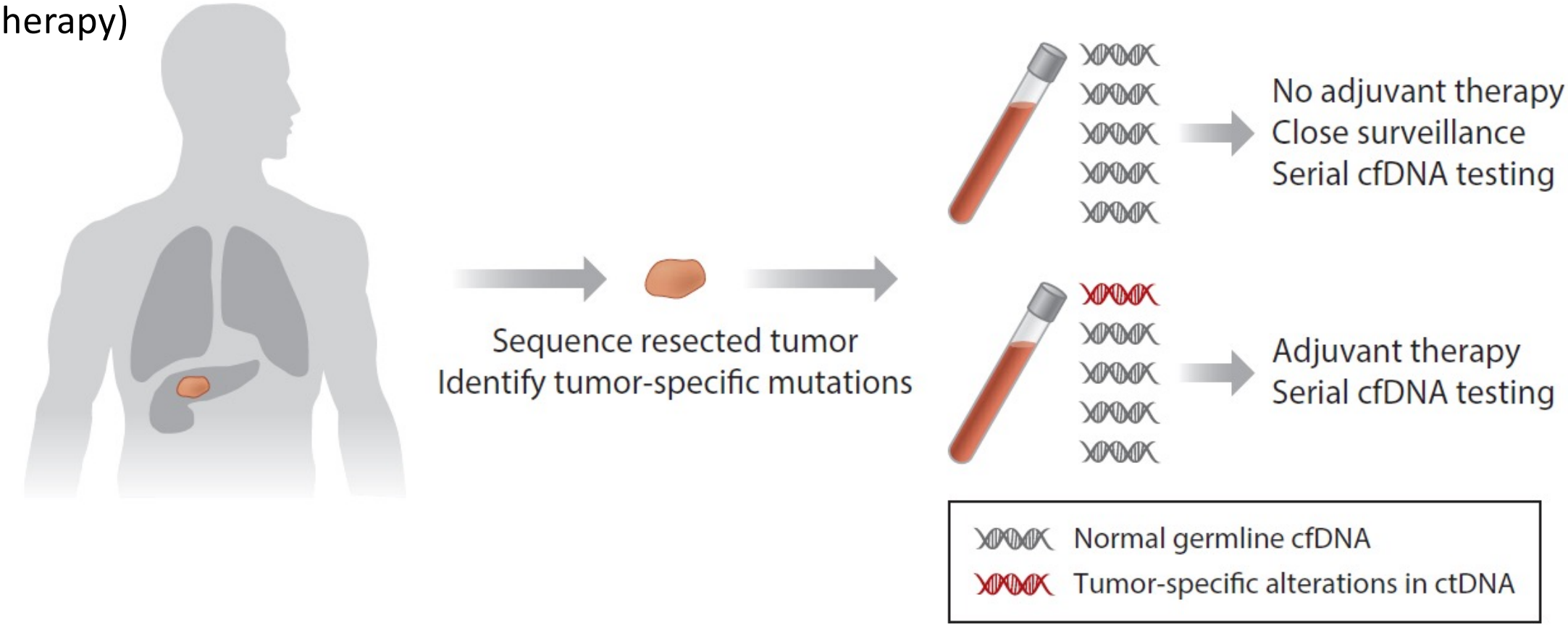
MRD TESTING FOR COLORECTAL CANCER

John Strickler, MD
Duke University
October 22, 2022

Can we integrate MRD into clinical care?

Potential applications:

- Selecting high risk patients for aggressive therapy when post-operative observation is SOC
- Spare patients chemotherapy/treatment if no residual disease (when SOC calls for additional therapy)



Morris and Strickler, Annu Rev Med. 2021. 72:399–413.

Stage I-III colon ca: Recurrence risk impacted by ctDNA status (tumor informed assay)

Relapse free survival

218 pts with stage I-III colon ca, monitored with Signatera assay

	Post-op ctDNA status	After end of adjuvant chemotherapy	Longitudinal monitoring (Q3 months for 3 yrs)
ctDNA positive	20%	17%	11%
ctDNA negative	87%	88%	97%

Henriksen et al., J Clin Oncol 39, 2021 (suppl 3; abstr 11)

GALAXY : Observational cohort from the CIRCULATE-Japan study

- CIRCULATE-Japan enrolled patients with resectable CRC (all stages) to evaluate the clinical utility of ctDNA MRD analysis
- CIRCULATE-Japan consists of 3 studies:
  - Observational cohort: GALAXY study
  - 2 randomized phase III trials (VEGA and ALTAIR trials)
- Blood samples are collected before surgery and 4, 12, 24, 36, 48, 72, and 96 weeks after surgery
- 1,564 patients enrolled in CIRCULATE-Japan
- 1,040 patients included in the GALAXY study
  - Median follow up time: 11.4 months
  - Data cutoff: 11/9/2021

Kotaka et. al., *Journal of Clinical Oncology* 40, no. 4_suppl (February 01, 2022) 9-9.

ctDNA detection at a single post-operative timepoint (4 weeks post op) is associated with poor prognosis

Disease free survival: Post-op-4w ctDNA status

712 pts with stage II-III colon ca, monitored with Signatera assay

ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
Negative	22/597	97.8% (96.3-98.7)	95.2% (92.6–96.9)
Positive	46/115	73.0% (63.9-80.2)	55.5% (44.8-65.0)

HR = 13.3
95% CI, 8.0 to 22.2, P<0.001

Sensitivity for recurrence= 68%

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Kotaka et. al., *Journal of Clinical Oncology* 40, no. 4_suppl (February 01, 2022) 9-9.

Adjuvant chemotherapy is not associated with improved DFS for patients with negative post-op ctDNA

Disease free survival: Negative post-op-4w ctDNA status

531 pts with high risk stage II/ stage III colon ca receiving adjuvant chemotherapy, monitored with Signatera assay

ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	7/214	98.6% (95.7-99.5)	96.2% (92.1–98.2)
W/O ACT	12/317	97.5% (95.0-98.7)	94.7% (90.5–97.1)

Adjusted HR = 1.3
95% CI, 0.5 to 3.6, P=0.63

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Kotaka et. al., *Journal of Clinical Oncology* 40, no. 4_suppl (February 01, 2022) 9-9.

DYNAMIC Study Design

Stage II Colon Cancer

- R0 resection
- ECOG 0 – 2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cancer

Plasma Collections
Week 4 + 7 post-op

R 2:1

ctDNA-Guided Management

- **ctDNA-Positive → Adjuvant Chemo** (oxaliplatin-based or single agent FP)
- **ctDNA-Negative → Observation**

ctDNA-Positive = Positive result at week 4 and/or 7

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Endpoints

Primary
- RFS rate at 2 years

Key Secondary
- Proportion receiving adjuvant chemo

Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M

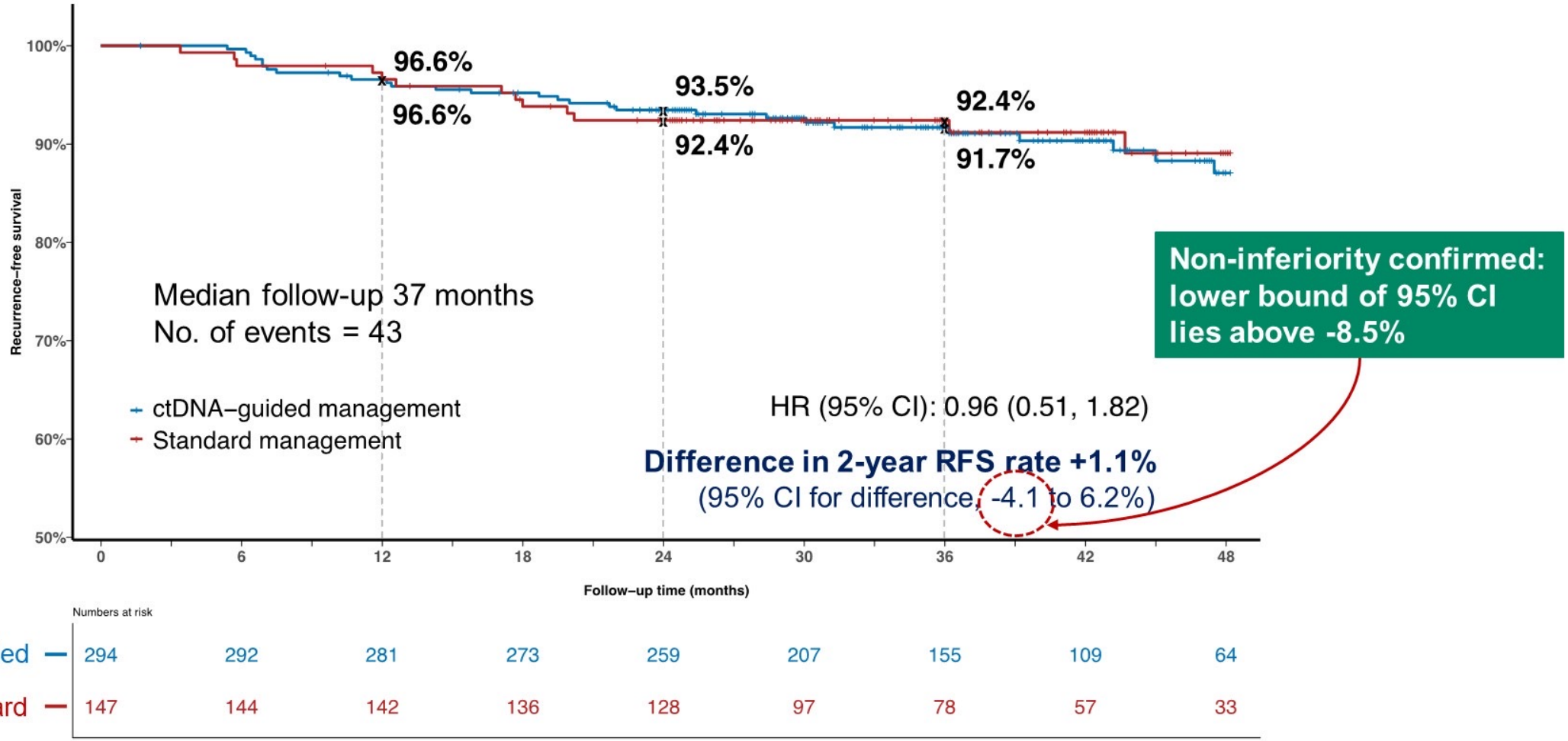
Tie et al., Presented at 2022 ASCO Annual Meeting

DYNAMIC: Adjuvant chemotherapy given less in the ctDNA-guided management group

Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 **(15%)**	41 **(28%)**	0.0017
Chemotherapy regimen received, n Oxaliplatin-based doublet Single agent fluoropyrimidine	 28/45 **(62%)** 17/45 **(38%)**	 4/41 **(10%)** 37/41 **(90%)**	 <.0001
Time from surgery to commencing chemotherapy, median (IQR), days	83 (76, 89)	53 (49, 61)	<.0001
Treatment duration, median (IQR), weeks	24 (19, 24)	24 (21, 24)	0.9318
Completed planned treatment, n	38 (85%)	32 (78%)	0.7036
Percentage of full dose delivered, median (IQR)	78 (56, 100)	84 (64, 100)	0.6194

Tie et al., Presented at 2022 ASCO Annual Meeting

DYNAMIC: RFS identical despite lower use of adjuvant chemotherapy for ctDNA guided management



Tie et al., Presented at 2022 ASCO Annual Meeting

MRD testing to guide patient management- Final thoughts

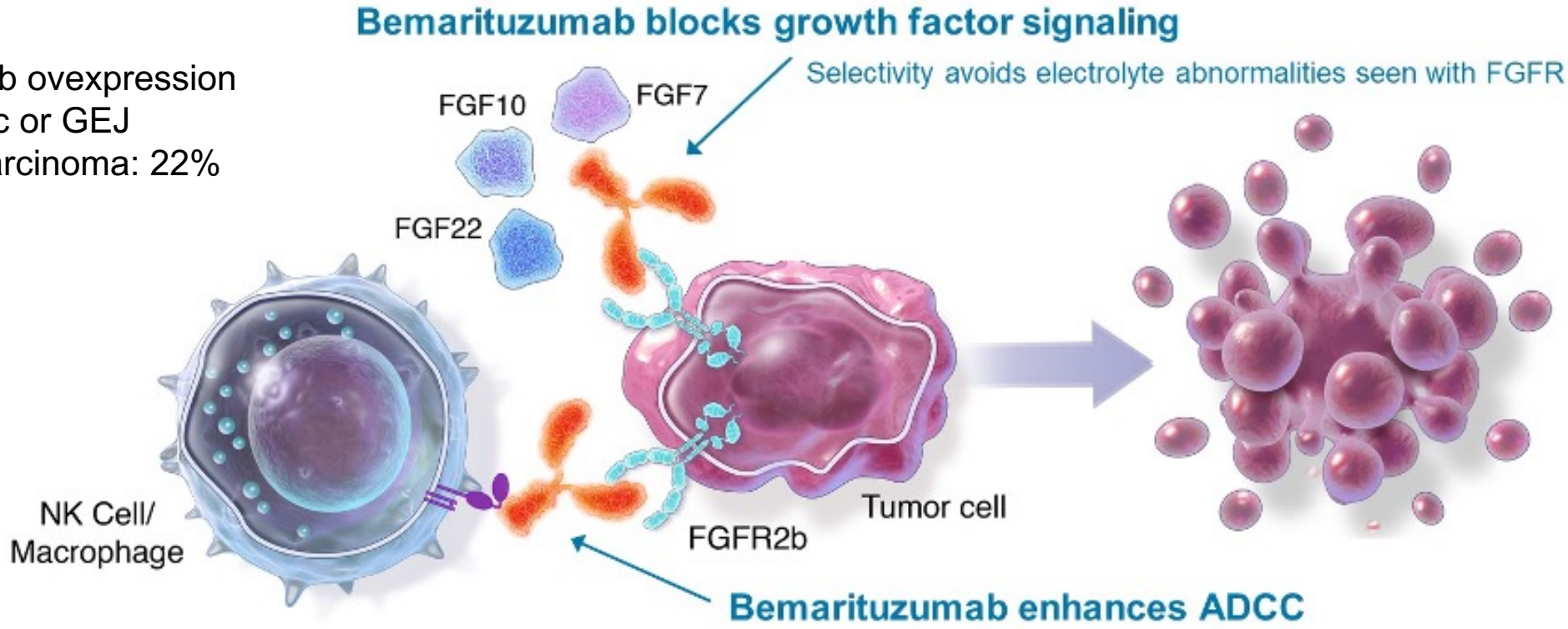
- MRD testing is a validated prognostic tool
  - Particularly valuable for patients with stage II disease
  - May have utility in patients with stage III disease
  - Other use cases (stage IV s/p resection, elevated CEA, etc)

- Rapid uptake in the clinic (ahead of the evidence) indicates that clinicians see an unmet need in CRC survivorship

- Prospective trials are ongoing to explore clinical utility of MRD testing… this is an area of rapid change

FGFR2b Overexpression in Gastric and Gastroesophageal Junction (GEJ) Cancer and Bemarituzumab Mechanism of Action

*FGFR2b ovexpression in gastric or GEJ adenocarcinoma: 22%



18% overall response rate in late-line FGFR2b+ gastroesophageal cancer[1]

ADCC, antibody-dependent cell-mediated cytotoxicity; FGF, fibroblast growth factor; IgG1, immunoglobulin G1; NK, natural killer; TKIs, tyrosine kinase inhibitors.

1. Catenacci D, et al. *J Clin Oncol*. 2020.

Catenacci DV et al. ASCO 2021;Abstract 4010. *Schrumpf T et al. PLOS ONE 2022;17(2):e0264011.

2021 ASCO ANNUAL MEETING

Abstract 4010

FIGHT: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 STUDY OF BEMARITUZUMAB (BEMA) COMBINED WITH MODIFIED FOLFOX6 IN 1L FGFR2B+ ADVANCED GASTRIC/GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA (GC) (NCT03694522)

Presenter: Daniel Catenacci, MD
University of Chicago

Authors: Catenacci DV[1], Kang YK[2], Saeed A[3], Yamaguchi K[4], Qin S[5], Lee KW[6], Kim IH[7], Oh SC[8], Li J[9], Turk HM[10], Teixeira AC[11], Borg C[12], Hitre E[13], Udrea AA[14], Cardellino GG[15], Guardeño Sanchez R[16], Mitra S[17], Yang Y[17], Enzinger PC[18], Wainberg ZA[19]

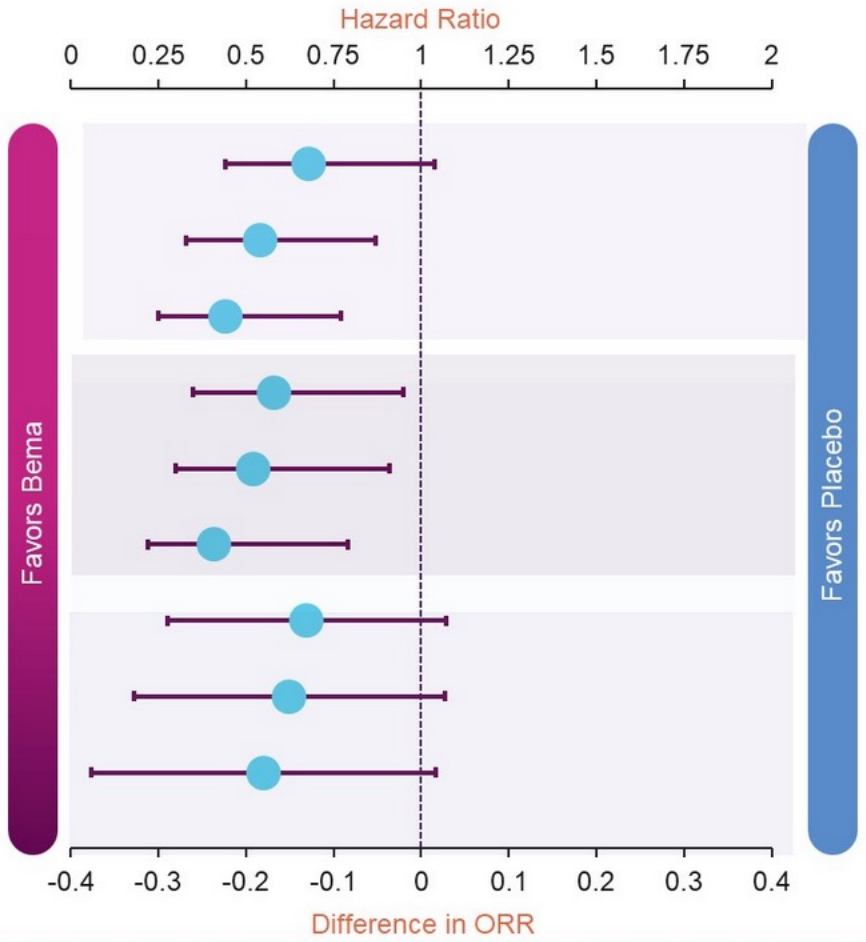
[1]University of Chicago, Chicago, USA; [2]Asan Medical Center, Seoul, South Korea; [3]Kansas University Cancer Center, Westwood, KS, USA; [4]The Cancer Institute Hospital of JFCR, Koto-Ku , Tokyo, Japan; [5]81 Hospital Nanjing University of Chinese Medicine, Nanjing, China; [6]Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Gyeonggi-do, South Korea; [7]The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea; [8]Korea University Guro Hospital, Seoul, South Korea; [9]Shanghai East Hospital, Shanghai, China; [10]Department of Medical Oncology, Bezmialem Vakif University, School of Medicine, Istanbul, Turkey; [11]Hospital Senhora Da Oliveira, Guimarães, Portugal; [12]Centre Hospitalier Régional Universitaire de Besançon, Besançon France; [13]National Institute of Oncology, Budapest, Hungary; [14]SC Medisprof SRL, Cluj-Napoca, Romania; [15]Department of Oncology, Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy; [16]Institut Català d'Oncologia, Girona, Spain; [17]FivePrime Therapeutics, Inc., South San Francisco, USA; [18]Dana Farber Cancer Institute, Boston, USA; [19]University of California, Los Angeles, USA

RTP RESEARCH TO PRACTICE

FIGHT: Efficacy of First-Line Bemarituzumab with Modified FOLFOX6 for Gastric/GEJ Adenocarcinoma

Endpoint	Subgroup	Median PFS/OS (months) Response rate	HR (95% CI) Difference in ORR (95% CI)
PFS	Overall*	Bema: 9.5 Placebo: 7.4	0.68 (0.44, 1.04)
	IHC 2+ or 3+ ≥5%†	Bema: 10.2 Placebo: 7.3	0.54 (0.33, 0.87)
	IHC 2+ or 3+ ≥10%‡	Bema: 14.1 Placebo: 7.3	0.44 (0.25, 0.77)
OS	Overall	Bema: NR Placebo: 12.9	0.58 (0.35, 0.95)
	IHC 2+ or 3+ ≥5%	Bema: NR Placebo: 12.5	0.52 (0.30, 0.91)
	IHC 2+ or 3+ ≥10%	Bema: NR Placebo: 11.1	0.41 (0.22, 0.79)
ORR	Overall	Bema: 36 (46.8%) Placebo: 26 (33.3%)	-13.1%§ (-29.0%, 2.8%)
	IHC 2+ or 3+ ≥5%	Bema: 30 (51.7%) Placebo: 22 (36.7%)	-15.1%§ (-32.8%, 2.7%)
	IHC 2+ or 3+ ≥10%	Bema: 24 (54.5%) Placebo: 19 (36.5%)	-18.0%§ (-37.7%, 1.7%)

*N = 155; †N = 118; ‡N = 96; §difference in ORR is calculated by (placebo ORR – Bema ORR).
NR, not reached.



ORR = overall response rate

- Median OS was reached in the overall population with longer follow-up – 5.7-mo improvement

Catenacci DV et al. ASCO 2021;Abstract 4010.

RTP RESEARCH TO PRACTICE

Ongoing Clinical Trials of Bemarituzumab

Study/Phase	Indications*	Key Overview	Clinicaltrials.gov Reference
FORTITUDE-101 Phase 3 Study (NCT05052801)	Untreated advanced gastric and GEJ cancer	**Bemarituzumab + mFOLFOX6 vs mFOLFOX6 alone** **Primary outcome:** Efficacy assessed by OS **Secondary outcomes:** Efficacy assessed by PFS and OR; safety and tolerability	https://clinicaltrials.gov/ct2/show/NCT05052801
FORTITUDE-102 Phase 1b/3 Study (NCT05111626)	Untreated advanced gastric and GEJ cancer	**Bemarituzumab + mFOLFOX6 + nivolumab (Part 2: comparison with mFOLFOX6 + nivolumab alone)** **Part 1 (phase 1b):** DLTs, TEAEs, clinically significant changes **Part 2 (phase 3):** Efficacy assessed by OS, PFS, OR	https://clinicaltrials.gov/ct2/show/NCT05111626
FORTITUDE-103 Phase 1 Study (NCT05322577)	Untreated advanced gastric and GEJ cancer	**Bemarituzumab + CAPOX, SOX, CAPOX + nivolumab, or SOX + nivolumab** **Primary outcomes**: Safety and tolerability assessed by DLTs, TEAEs **Secondary outcomes**: Efficacy assessed by OR, DOR, PFS, OS, and pharmacokinetics	https://clinicaltrials.gov/ct2/show/NCT05322577
FORTITUDE-201 Phase 1b/3 Study (NCT05267470)	Squamous-cell non-small-cell lung cancer	**Bemarituzumab + docetaxel (Part 3: bemarituzumab monotherapy)** **Part 1:** Dose exploration assessed by DLTs and TEAEs **Part 2:** Part 1 identified dose safety assessed by TEAEs **Part 3:** Safety assessed by TEAEs	https://clinicaltrials.gov/ct2/show/NCT05267470
FORTITUDE-301 Phase 1b/2 Study (NCT05325866)	Solid tumors	**Bemarituzumab monotherapy** **Part 1:** Dose exploration assessed by DLTs, TEAEs **Part 2:** Part 1 identified dose efficacy assessed by OR	https://clinicaltrials.gov/ct2/show/NCT05325866

*In FGFR2b overexpressed tumors.

CAPOX, capecitabine + oxaliplatin; DLT, dose-limiting toxicity; DOR, duration of response; FGFR2b, fibroblast growth factor receptor 2b; GEJ, gastroesophageal junction; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; OR, objective response; OS, overall survival; SOX, S-1 + oxaliplatin; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

Smyth E et al. ASCO 2022;Abstract TPS4164.

RTP RESEARCH TO PRACTICE

Pancreatic Cancer

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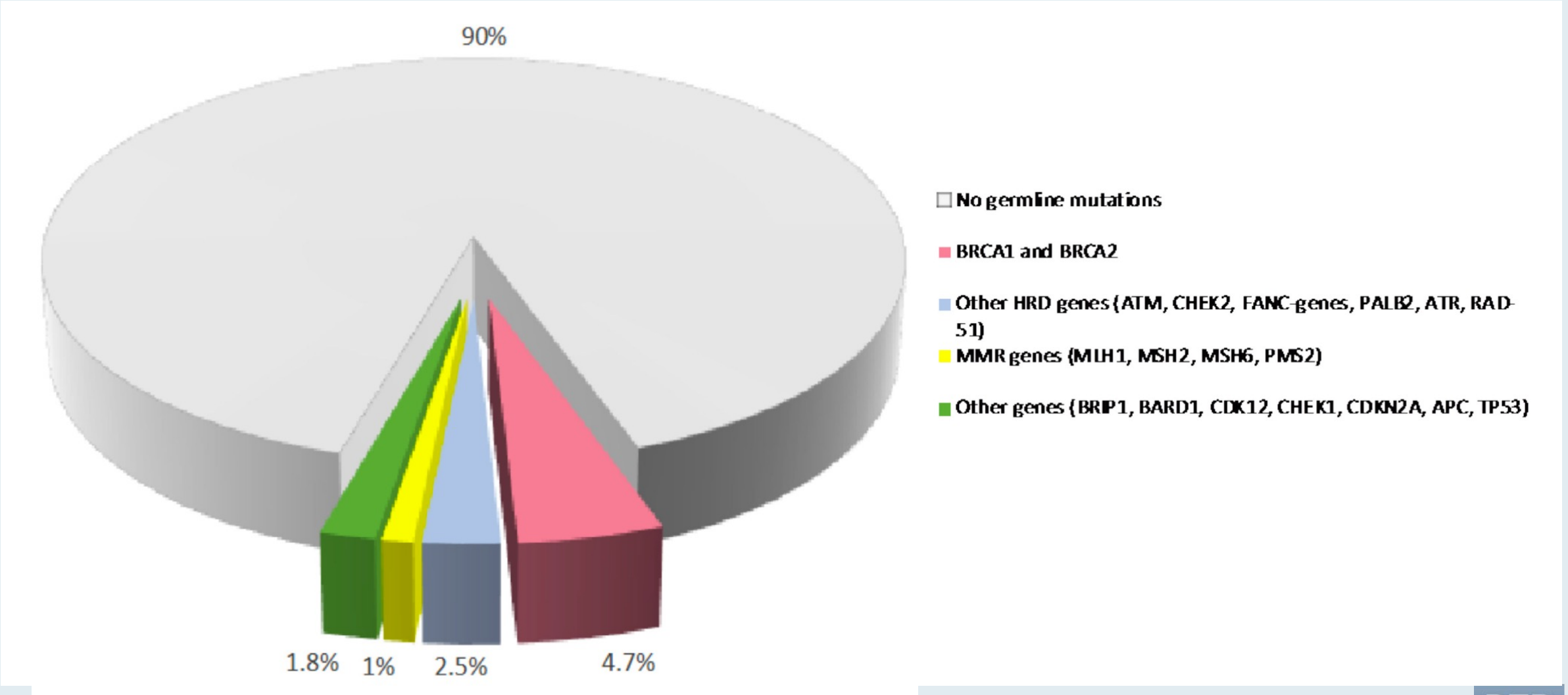
Prevalence of Germline Aberrations in Cancer Susceptibility Genes in Pancreatic Ductal Adenocarcinoma



Casolino R et al. *Cancers* 2022;14:3239.

original reports

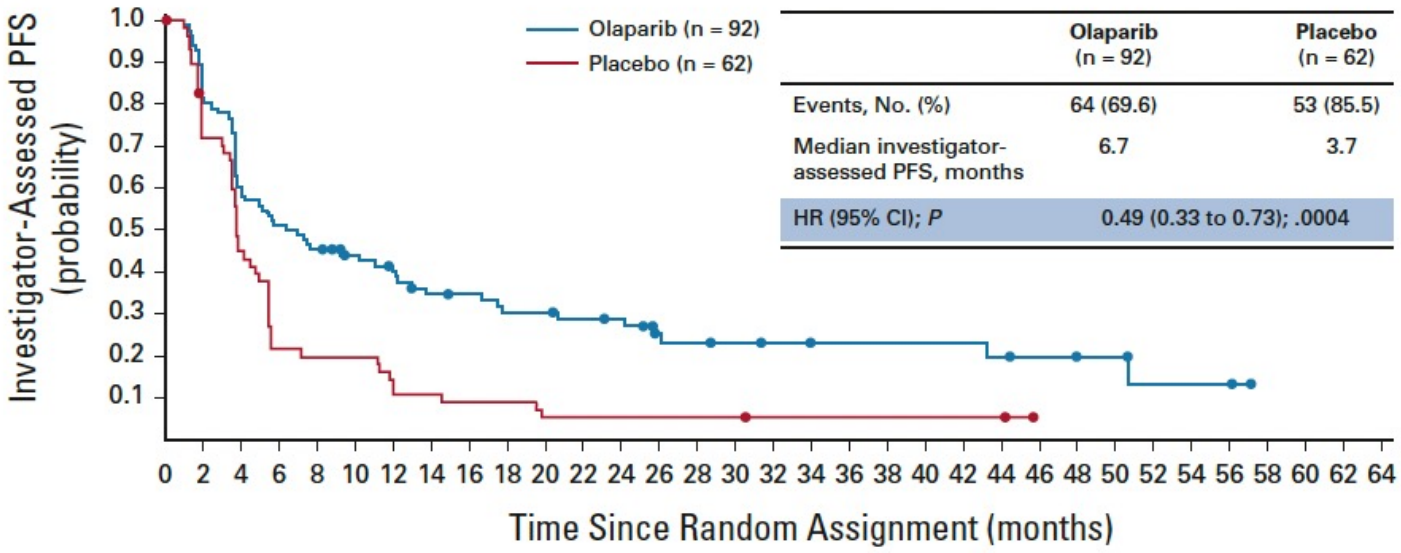
Overall Survival Results From the POLO Trial: A Phase III Study of Active Maintenance Olaparib Versus Placebo for Germline BRCA-Mutated Metastatic Pancreatic Cancer

Hedy L. Kindler, MD[1]; Pascal Hammel, MD, PhD[2]; Michele Reni, MD[3]; Eric Van Cutsem, MD, PhD[4]; Teresa Macarulla, MD, PhD[5]; Michael J. Hall, MD[6]; Joon Oh Park, MD, PhD[7]; Daniel Hochhauser, MD, PhD[8]; Dirk Arnold, MD, PhD[9]; Do-Youn Oh, MD, PhD[10]; Anke Reinacher-Schick, MD, PhD[11]; Giampaolo Tortora, MD, PhD[12]; Hana Algül, MD, PhD, MPH[13]; Eileen M. O'Reilly, MD[14]; Sonal Bordia, MD[15]; David McGuinness, MSc[16]; Karen Cui, MD, PhD[17]; Gershon Y. Locker, MD[17]; and Talia Golan, MD[18]

J Clin Oncol 2022 July 14;[Online ahead of print].

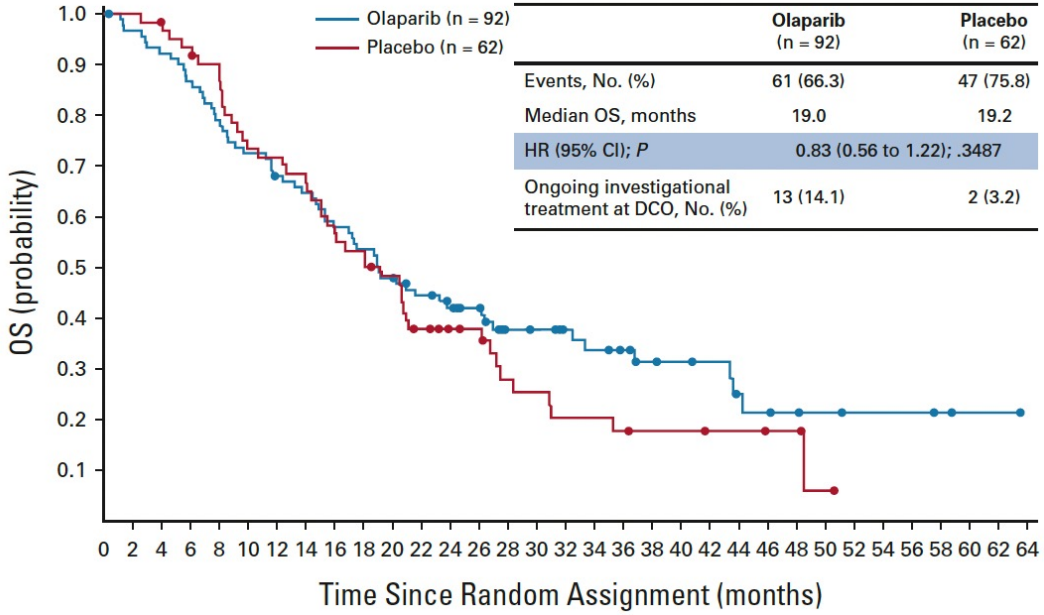
POLO: Survival Analyses

Progression-Free Survival



	Olaparib (n = 92)	Placebo (n = 62)
Events, No. (%)	64 (69.6)	53 (85.5)
Median investigator-assessed PFS, months	6.7	3.7
HR (95% CI); *P*	0.49 (0.33 to 0.73); .0004	

Overall Survival



	Olaparib (n = 92)	Placebo (n = 62)
Events, No. (%)	61 (66.3)	47 (75.8)
Median OS, months	19.0	19.2
HR (95% CI); *P*	0.83 (0.56 to 1.22); .3487	
Ongoing investigational treatment at DCO, No. (%)	13 (14.1)	2 (3.2)

DCO = data cutoff

Kindler HL et al. *J Clin Oncol* 2022 July 14;[Online ahead of print].

Thank you for joining us!

CME, MOC and NCPD credit information will be emailed to each participant within 5 business days.

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