Flabbergasted by Gastroesophageal Evolving Therapies

Afsaneh Barzi, MD, PhD

Associate Professor of Oncology

Medical Director of Value and Quality AccessHope

Disclosures

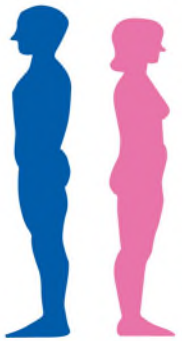
- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Epidemiology

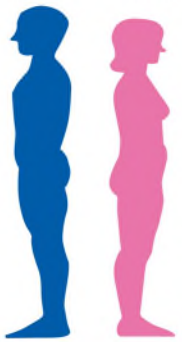
Estimated New Cases

Males			Females		
Prostate	288,300	29%	Breast	297,790	31%
Lung & bronchus	117,550	12%	Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%	Colon & rectum	71,160	8%
Urinary bladder	62,420	6%	Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%	Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%	Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%	Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%	Pancreas	30,920	3%
Leukemia	35,670	4%	Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%	Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**	**All Sites**	**948,000**	**100%**



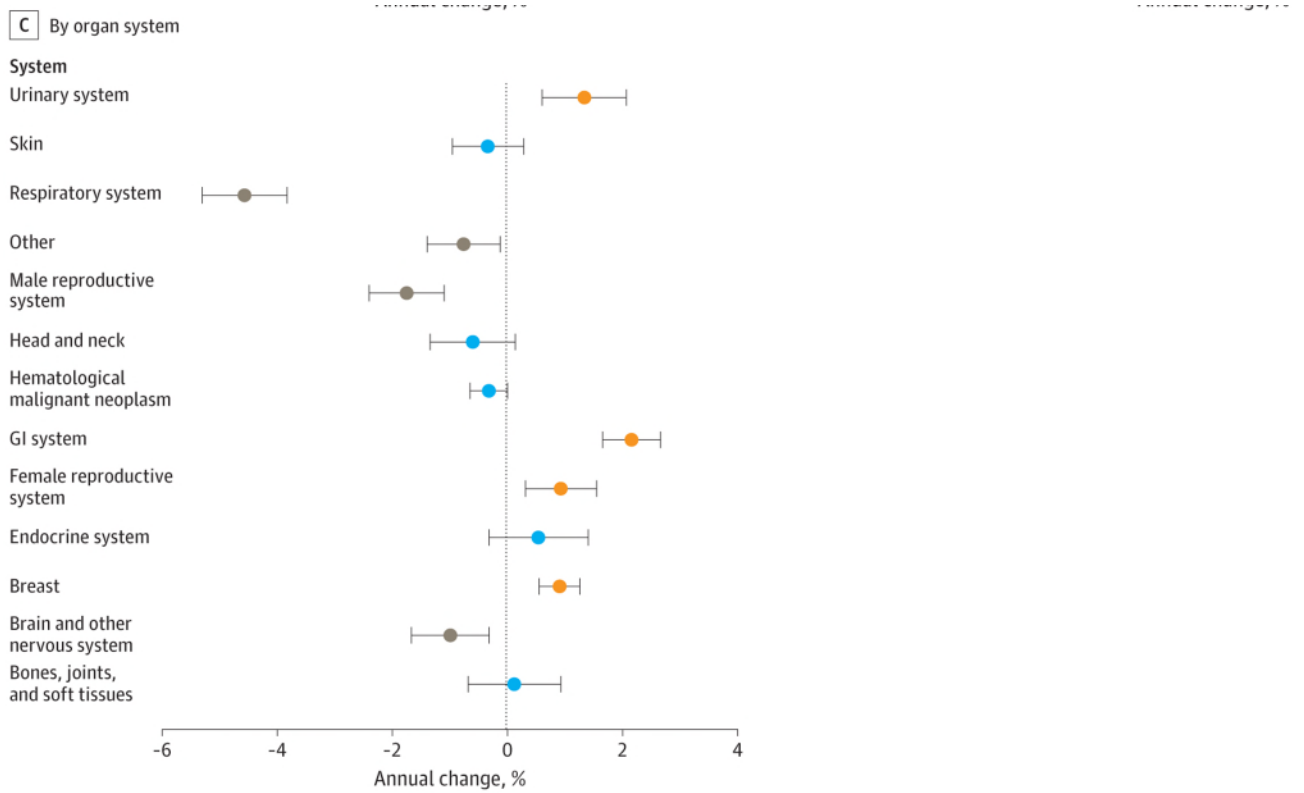
Estimated Deaths

Males			Females		
Lung & bronchus	67,160	21%	Lung & bronchus	59,910	21%
Prostate	34,700	11%	Breast	43,170	15%
Colon & rectum	28,470	9%	Colon & rectum	24,080	8%
Pancreas	26,620	8%	Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%	Ovary	13,270	5%
Leukemia	13,900	4%	Uterine corpus	13,030	5%
Esophagus	12,920	4%	Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%	Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%	Brain & other nervous system	7,970	3%
All Sites	**322,080**	**100%**	**All Sites**	**287,740**	**100%**



CA A Cancer J Clinicians, Volume: 73, Issue: 1, Pages: 17-48, First published: 12 January 2023, DOI: (10.3322/caac.21763)

Rising Incidence in Young Adults



Koh B, et al. JAMA Netw Open. 2023;6(8):e2328171.

Objective

- Evolution of treatment of metastatic disease by histology
    - Current standards
    - Emerging therapies
- Targeted therapies in early-stage disease

Combination Chemotherapy

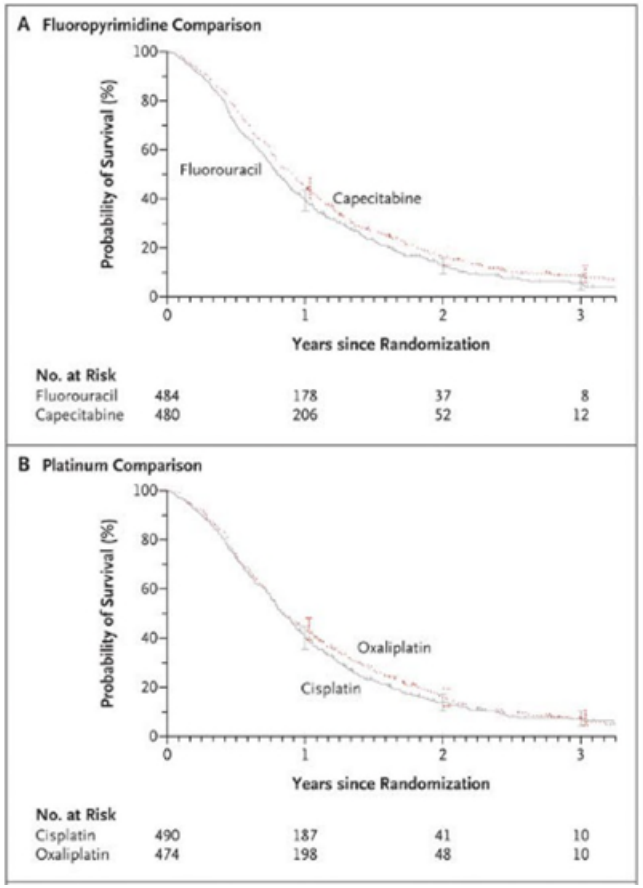


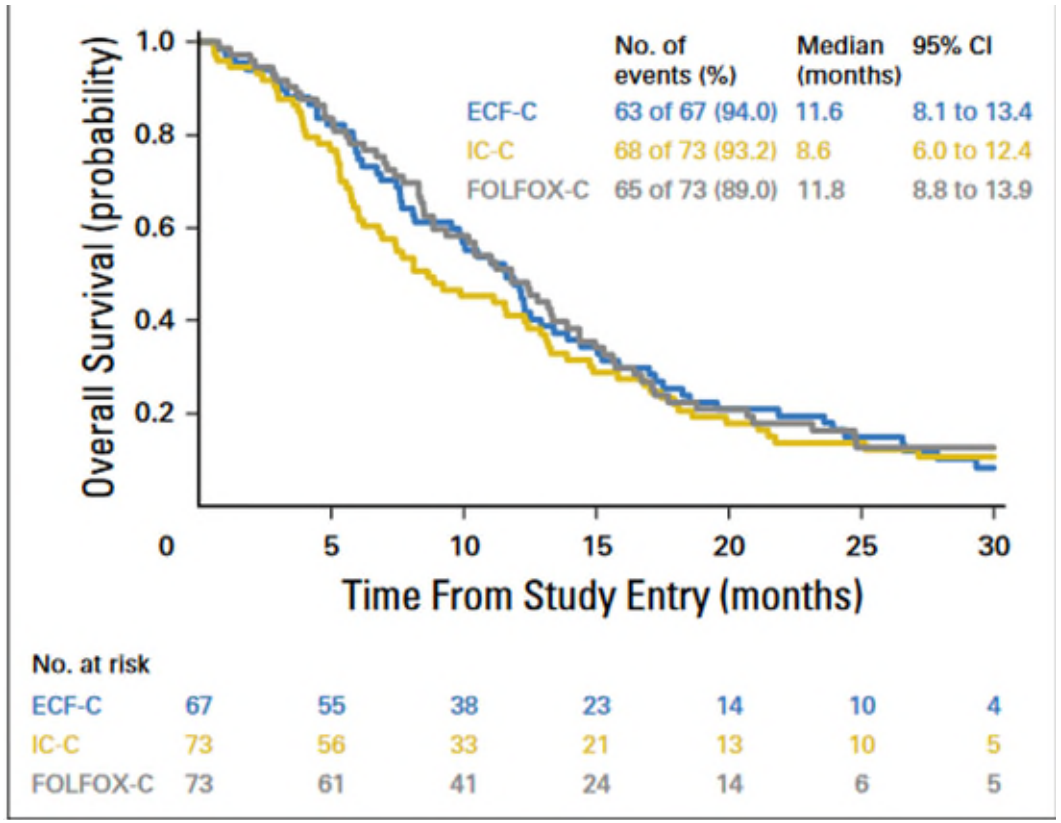
Table 2. Analysis of Efficacy (Intention-to-Treat Population).*

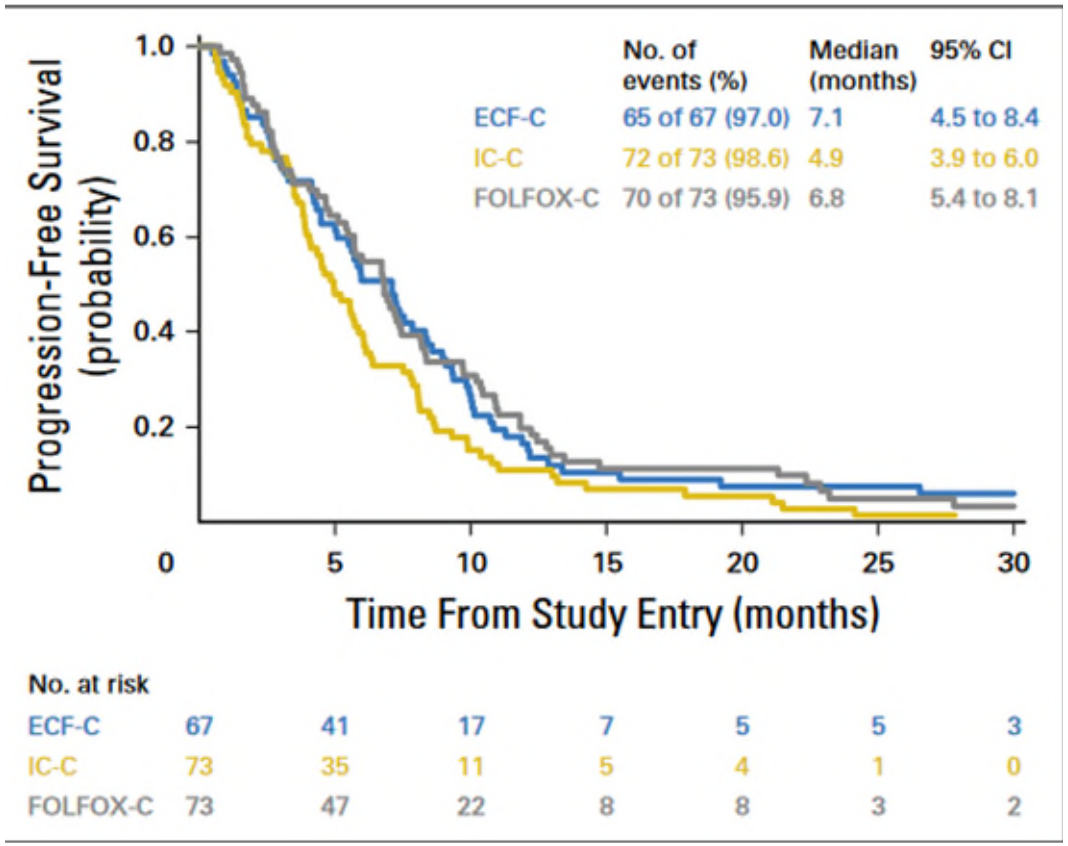
Variable	ECF (N=263)	ECX (N=250)	EOF (N=245)	EOX (N=244)
Death				
No. of patients	225	213	213	199
Hazard ratio (95% CI)		0.92 (0.76–1.11)	0.96 (0.79–1.15)	0.80 (0.66–0.97)
P value		0.39	0.61	0.02
Overall survival				
Median — mo	9.9	9.9	9.3	11.2
At 1 yr — % (95% CI)	37.7 (31.8–43.6)	40.8 (34.7–46.9)	40.4 (34.2–46.5)	46.8 (40.4–52.9)
Progression-free survival				
Median — mo	6.2	6.7	6.5	7.0
Patients who had progression or died	237	231	221	213
Hazard ratio (95% CI)		0.98 (0.82–1.17)	0.97 (0.81–1.17)	0.85 (0.70–1.02)
P value		0.80	0.77	0.07
Response				
Overall — % (95% CI)†	40.7 (34.5–46.8)	46.4 (40.0–52.8)	42.4 (36.1–48.8)	47.9 (41.5–54.3)
Complete — %	4.1	4.2	2.6	3.9
Partial — %	36.6	42.2	39.8	44.0
P value		0.20	0.69	0.11

* Patients were randomly assigned to receive one of four triplet therapies: epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX), or epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX).
† Overall response could be evaluated in 246 patients in the ECF group, 237 patients in the ECX group, 231 patients in the EOF group, and 234 patients in the EOX group.

Cunningham D et al. N Engl J Med 2008;358:36-46.

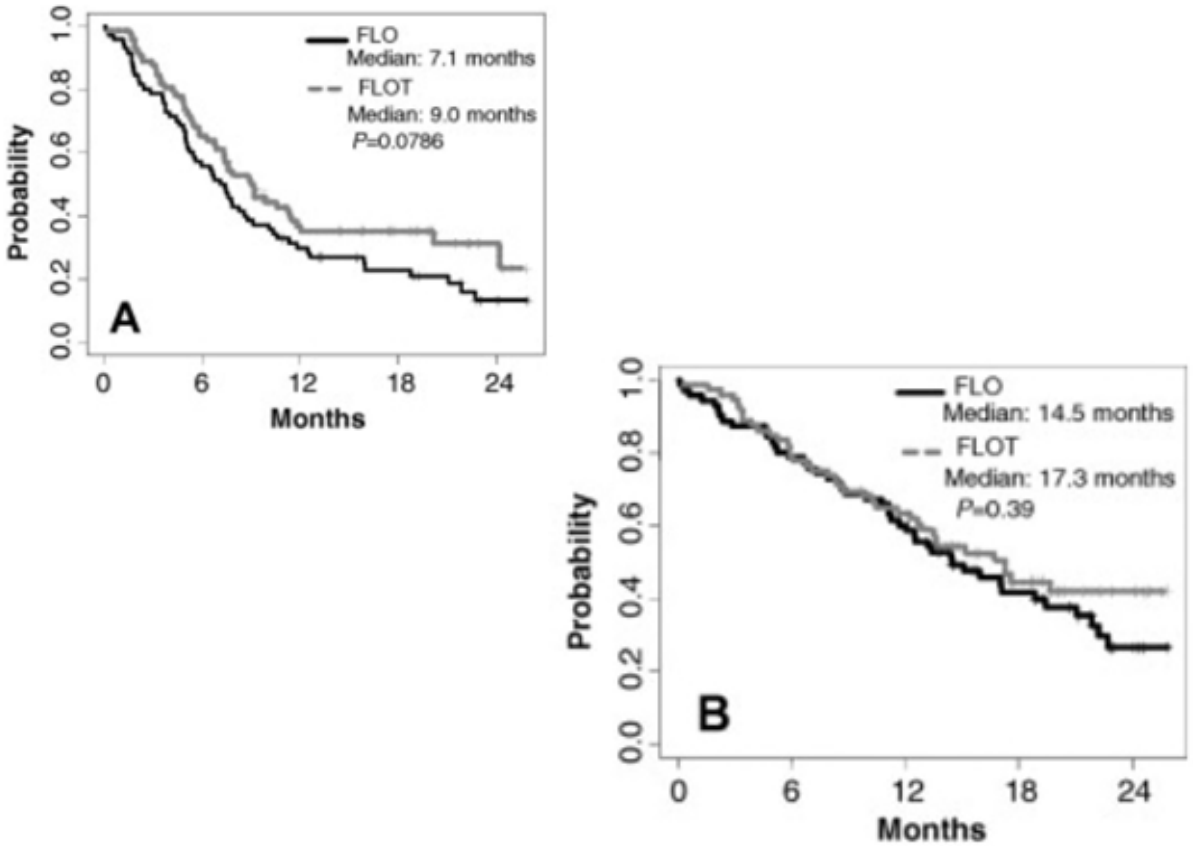
FOLFOX Evolves as Standard





Enzinger P et al. JCO 2016 Aug 10;34(23):2736-42.

Triplet Therapy (not an established standard)



ASCO GI, 2018

A phase II trial of first-line FOLFIRINOX for patients with advanced gastroesophageal adenocarcinoma.

- ORR was 78% (38/49) in all patients, 67% (18/27) in HER2 (neg).
- Median PFS is 11.9 months.
- Median OS is 17.4 months and median follow up time 16.1 months.
- 41 (83.7%) had dose modification or delay during treatment. There were no unexpected toxicities.

Al-Batran S et al. European Journal of Cancer, Mar 2013, 835-842

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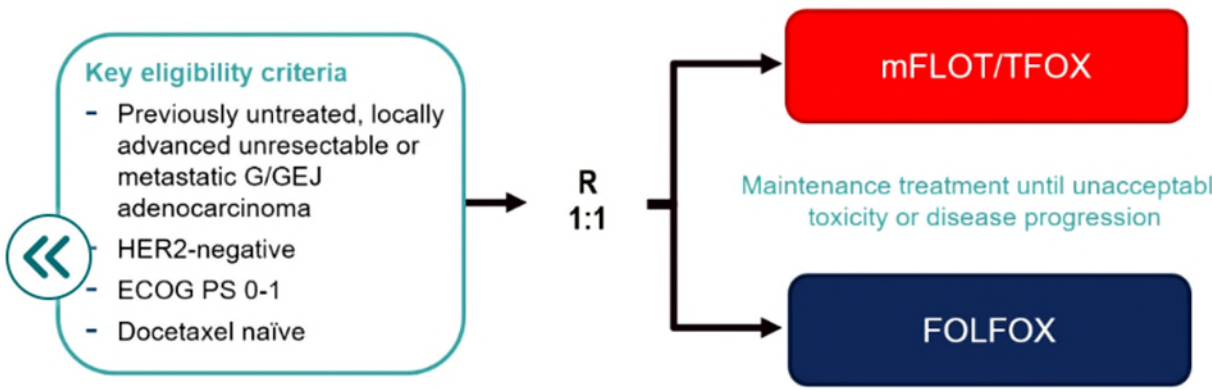
GASTFOX-PRODIGE 51

Study Design

Randomized, multicenter, academic, phase III trial



Stratification factors:

ECOG PS (0 vs 1),
prior (neo)adjuvant (yes vs no),
tumor stage (LA vs metastatic),
tumor location (G vs GEJ),
pathological subtype
(signet ring cell : yes vs no)

Recruitment period : between December 2016 and December 2022 (96 French cancer centers)

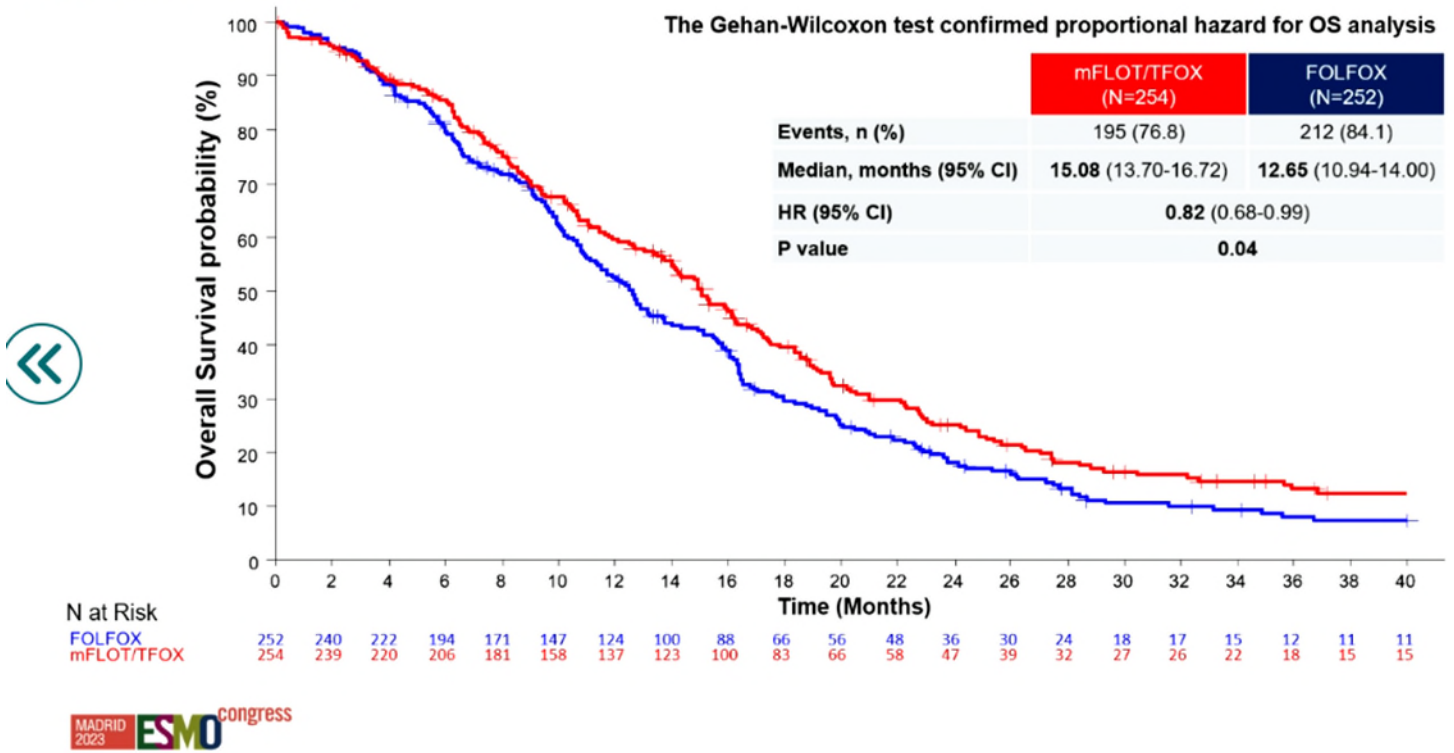
Data cutoff date for PFS and OS analysis : June 2023

Median follow up : 42.8 months

GASTFOX-PRODIGE 51

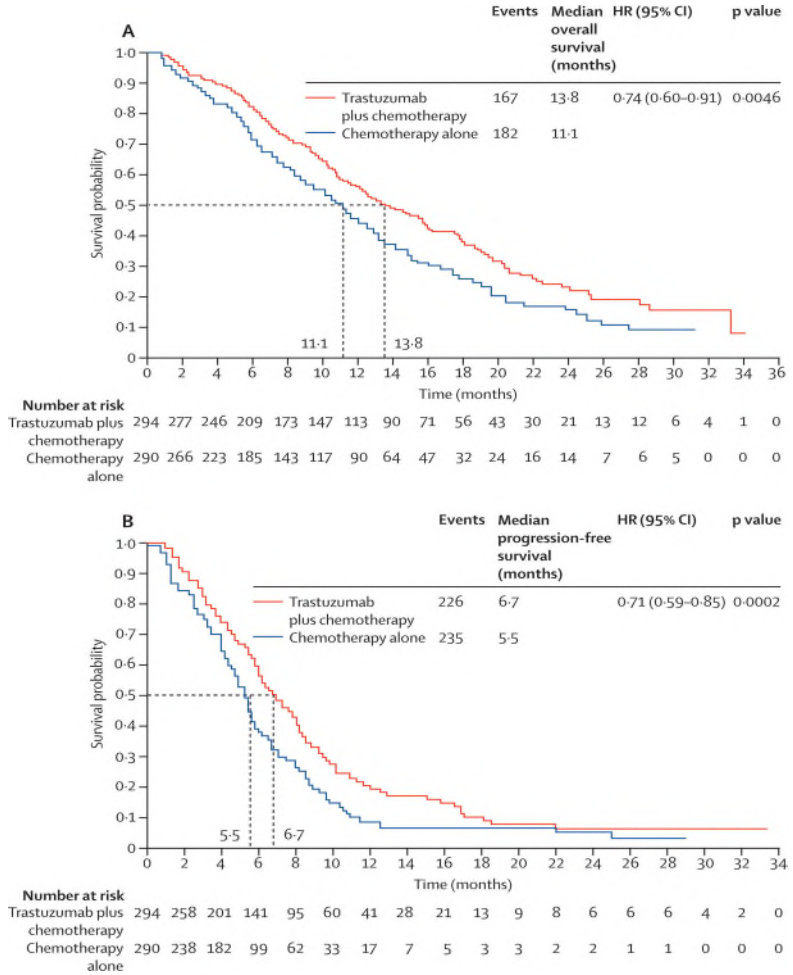
Overall survival

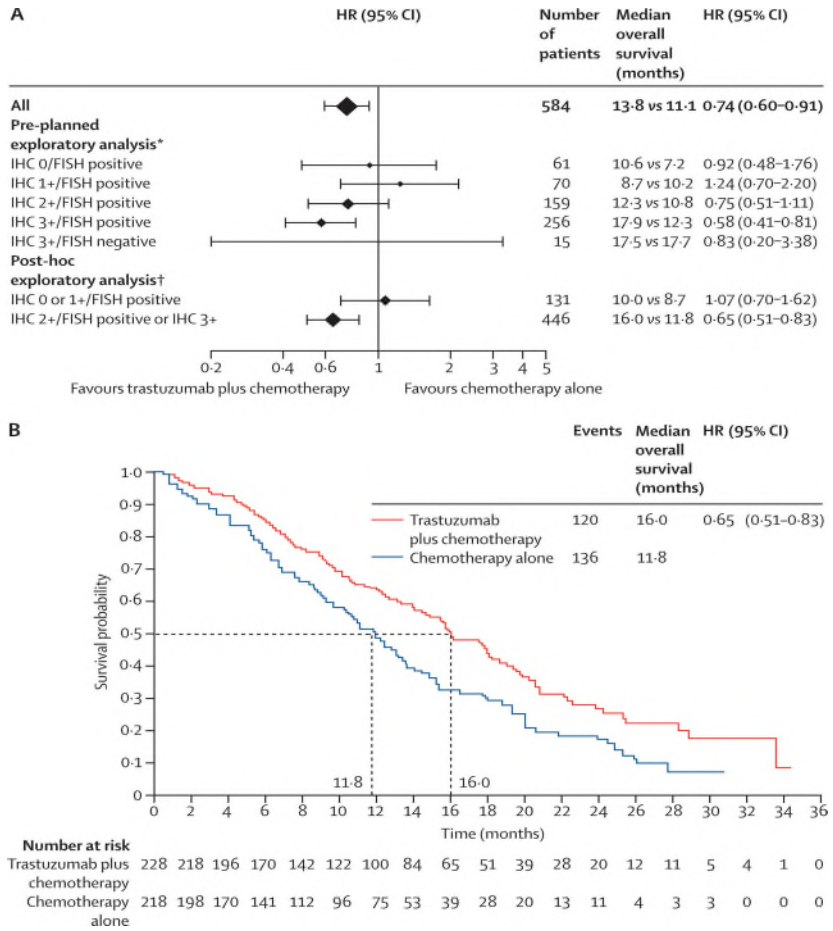
Intention-to-treat (ITT)



MADRID 2023 ESMO congress

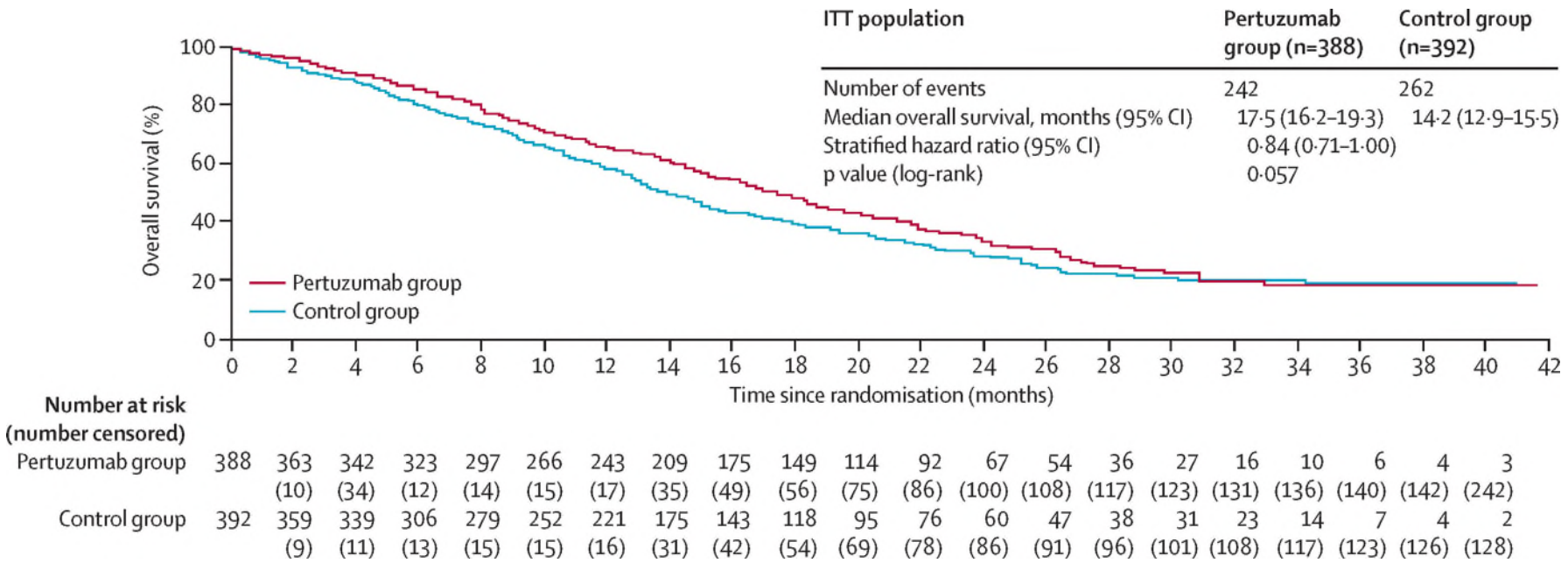
Trastuzumab





Bang Y et al. *The Lancet* 2010 376687-697

JACOB Trial



Tabernero J et al. *The Lancet Oncology* 2018 191372-1384

KEYNOTE-811

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

Variable	Pembrolizumab group (*n* = 133)	Placebo group (*n* = 131)
Objective response (% (95% confidence interval))[a]	74.4 (66.2–81.6)	51.9 (43.0–60.7)
Disease control (% (95% confidence interval))[b]	96.2 (91.4–98.8)	89.3 (82.7–94.0)
Best overall response (number (%))		
Complete response	15 (11.3)	4 (3.1)
Partial response	84 (63.2)	64 (48.9)
Stable disease	29 (21.8)	49 (37.4)
Progressive disease	5 (3.8)	7 (5.3)
Not evaluable[c]	0 (0.0)	2 (1.5)
Not assessed[c]	0 (0.0)	5 (3.8)

Janjigian Y et al. *Nature* volume 600, pages727–730 (2021)

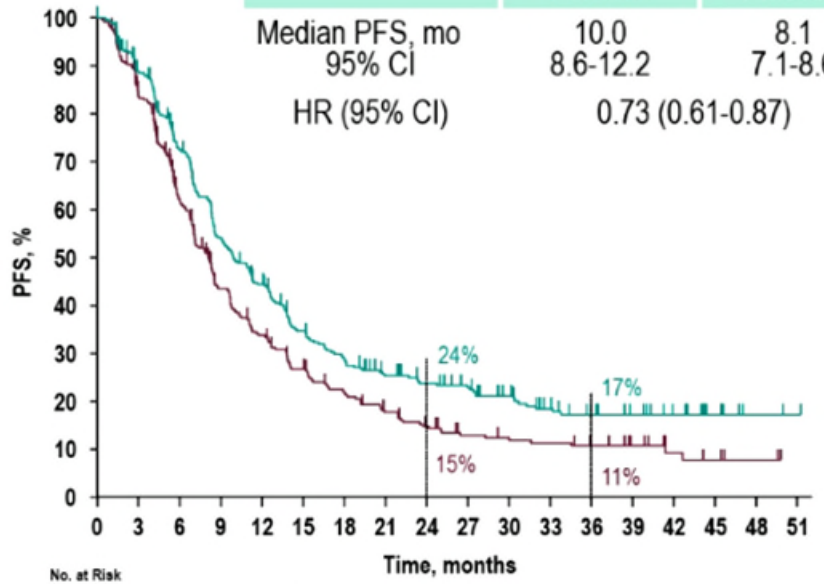
KEYNOTE-811 (ESMO 2023)

Progression-Free Survival at IA3: 38.5 months of follow-up[a]

RECIST V1.1, BICR

All patients

	Pembro	Placebo
Median PFS, mo	10.0	8.1
95% CI	8.6-12.2	7.1-8.6
HR (95% CI)	0.73 (0.61-0.87)	

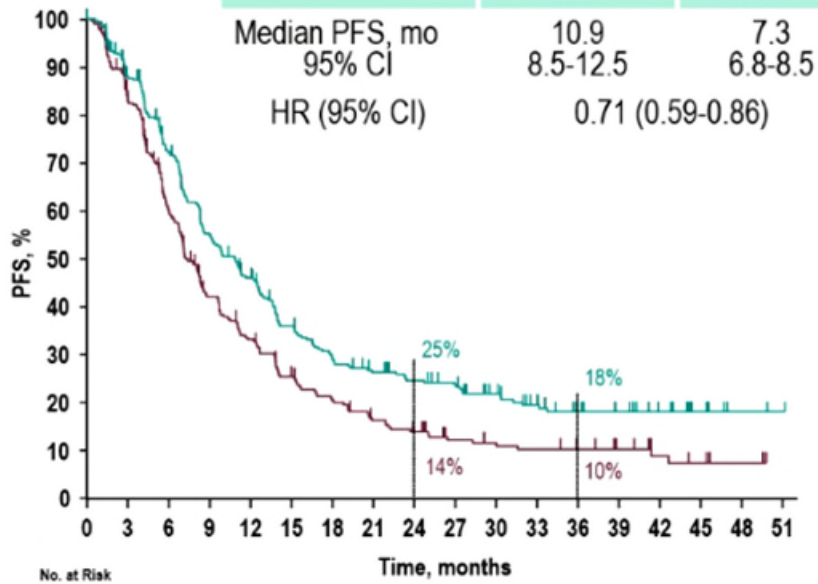


No. at Risk

Pembrolizumab gp	350	296	234	173	139	102	84	67	59	53	41	31	24	20	14	6	2	1
Placebo gp	348	274	184	121	93	71	55	43	34	25	23	21	17	11	6	4	2	0

PD-L1 CPS ≥1[b]

	Pembro	Placebo
Median PFS, mo	10.9	7.3
95% CI	8.5-12.5	6.8-8.5
HR (95% CI)	0.71 (0.59-0.86)	

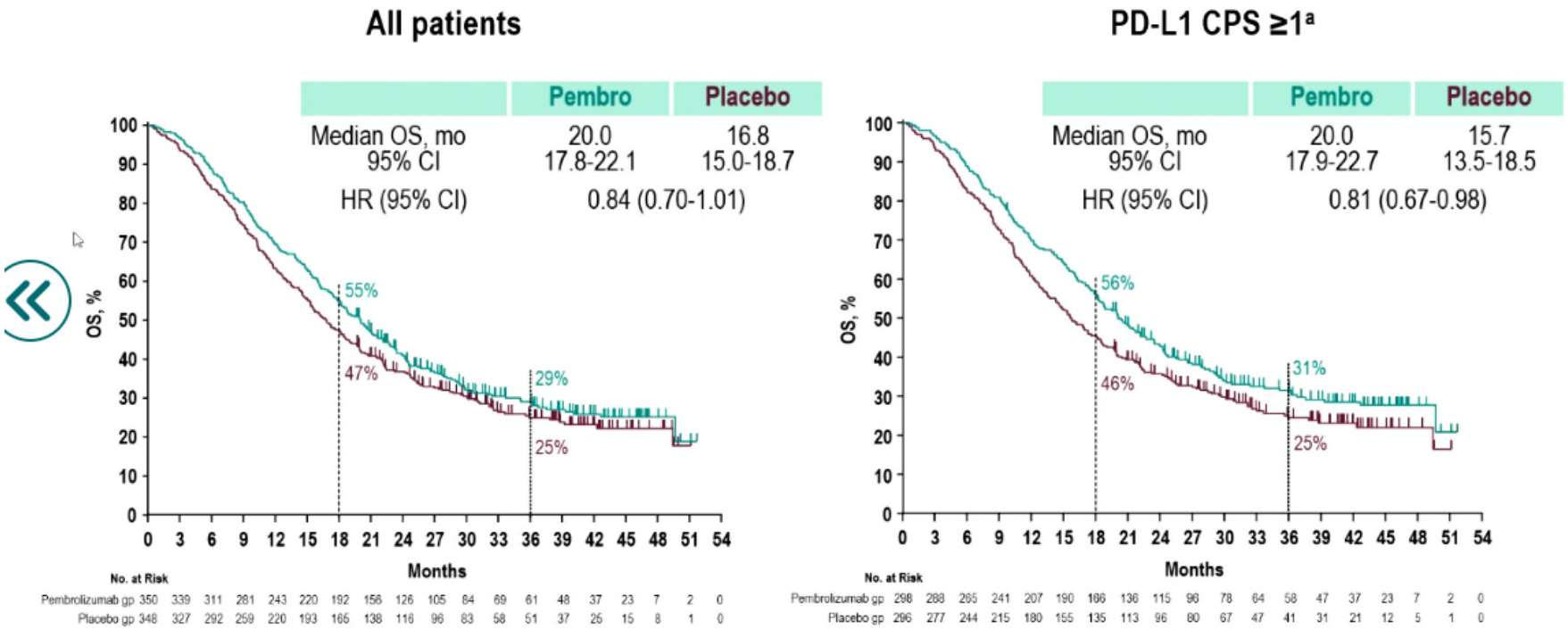


No. at Risk

Pembrolizumab gp	298	250	200	151	123	91	74	63	56	51	39	30	23	20	14	6	2	1
Placebo gp	296	231	152	100	78	58	45	34	28	20	18	16	14	10	6	4	2	0

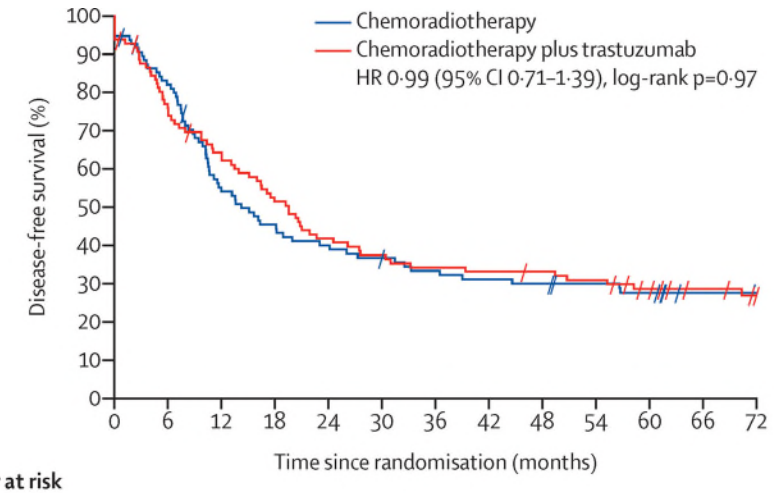
Data cut-off: March 29, 2023. [a]Median follow-up. [b]Not a prespecified endpoint.

KEYNOTE-811 (ESMO 2023)

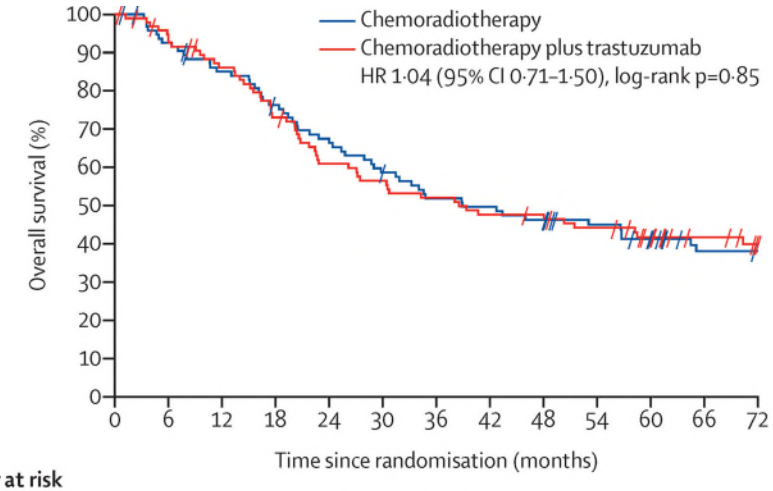


Data cut-off: March 29, 2023. OS did not meet the prespecified criteria for significance at IA3 and will be retested at final analysis. [a]Not a prespecified endpoint.

RTOG-1010



Number at risk (number censored)							
Chemoradiotherapy	96 (0)	51 (3)	37 (3)	30 (4)	27 (4)	23 (6)	18 (11)
Chemoradiotherapy plus trastuzumab	98 (0)	60 (4)	39 (4)	32 (4)	30 (5)	23 (8)	14 (16)



Number at risk (number censored)							
Chemoradiotherapy	96 (0)	78 (4)	61 (5)	46 (6)	41 (6)	30 (13)	23 (18)
Chemoradiotherapy plus trastuzumab	98 (0)	79 (6)	55 (7)	47 (7)	42 (8)	32 (13)	19 (25)

Safran H et al. *The Lancet Oncology* 2022 23259-269

PETRARCA Study Design
Randomized, multicenter, investigator-initiated, phase II/III trial

- Esophagogastric adenocarcinoma
- cT2-4 cN_{any} cM0 *or* T_{any} cN+ cM0
- HER2-positivity (centrally assessed)
- ECOG ≤ 2

Stratification factors
- ECOG (0 or 1 vs. 2)
- Location of primary (GE-junction vs. stomach)
- Age (< 60 vs. 60-69 vs. ≥70 years)

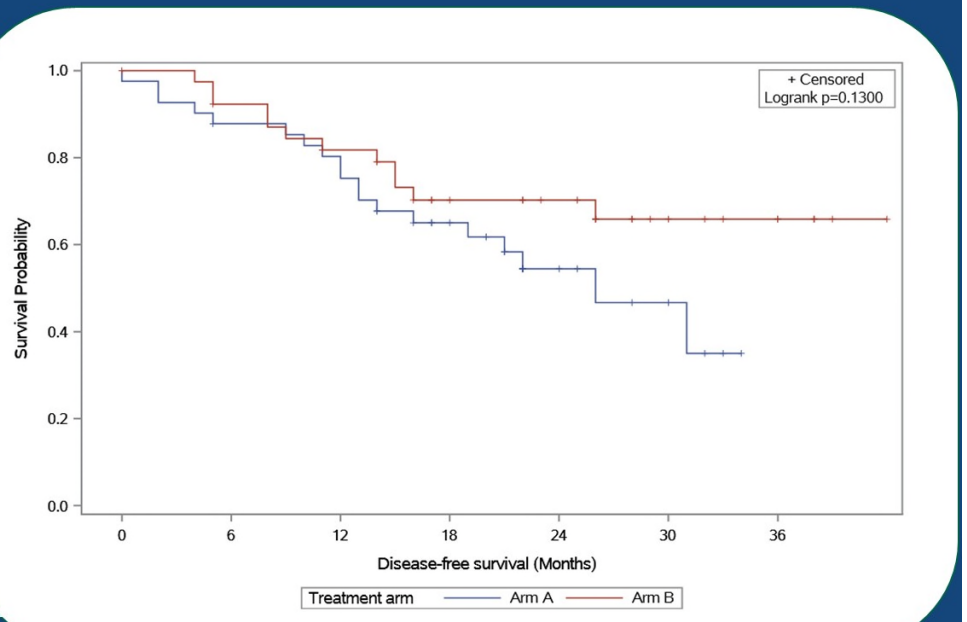
R

FLOT x4
↓
Resection
↓
FLOT x 4

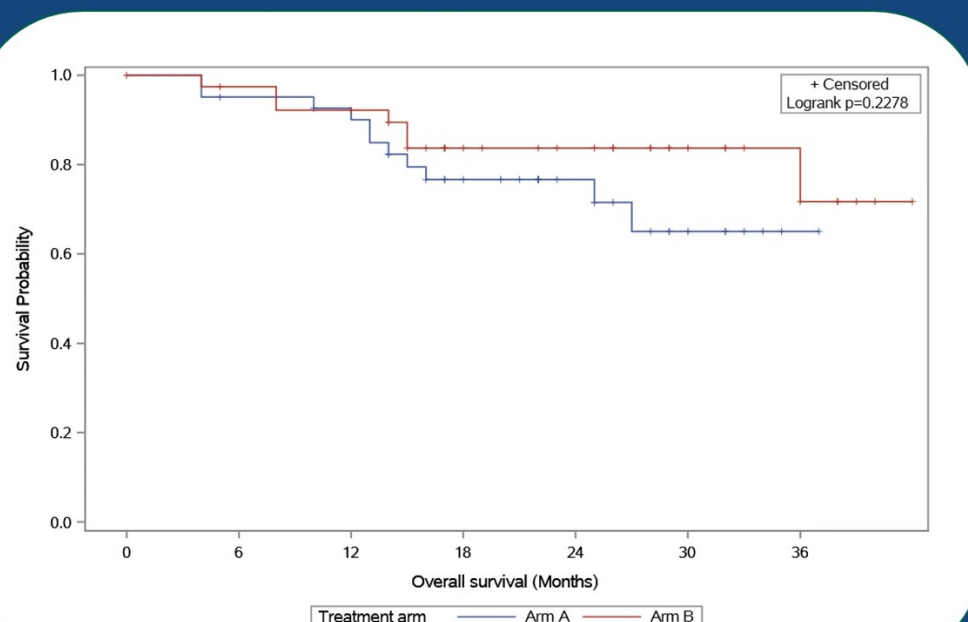
FLOT x 4 + Tras + Per
↓
Resection
↓
FLOT x 4 + Tras + Per
↓
Tras + Per (9 cycles 3-weekly)

PETRARCA

Disease-free Survival (DFS)

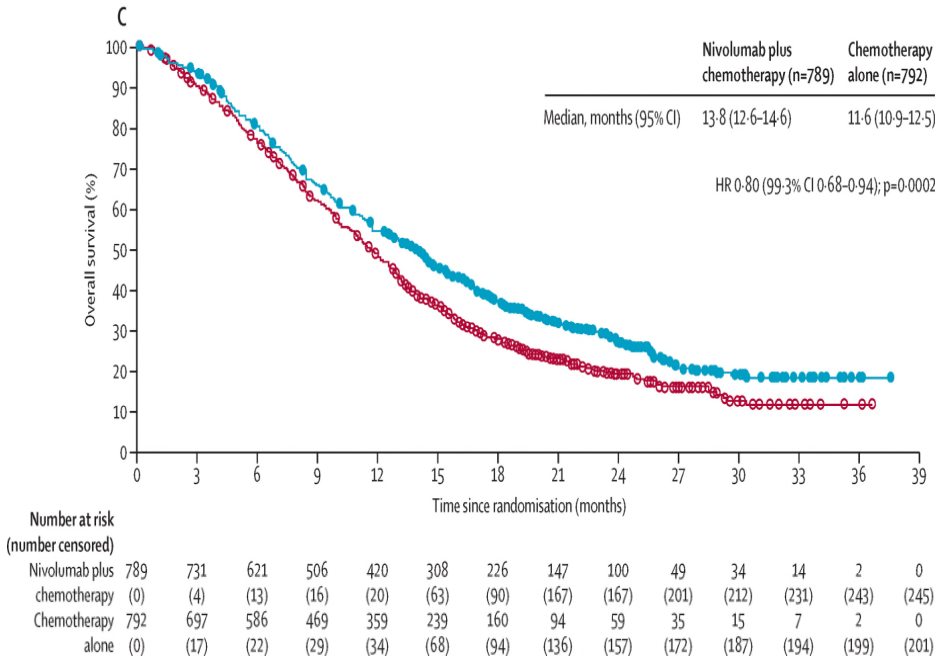


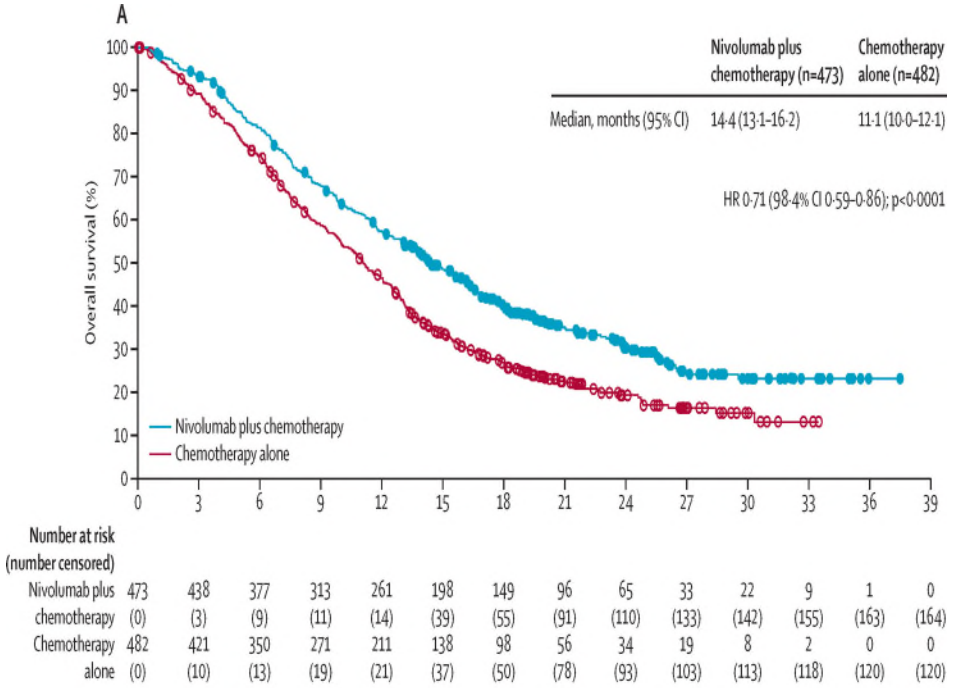
Overall Survival (OS)



Hofheinz R et al. *ASCO 2020*

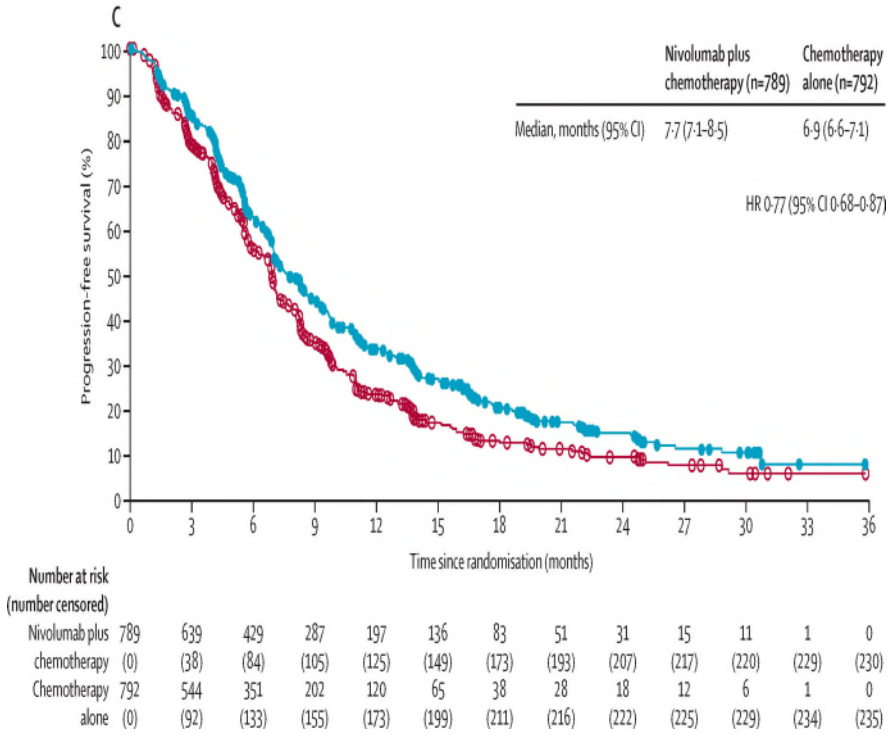
FOLFOX/Nivolumab (OS)

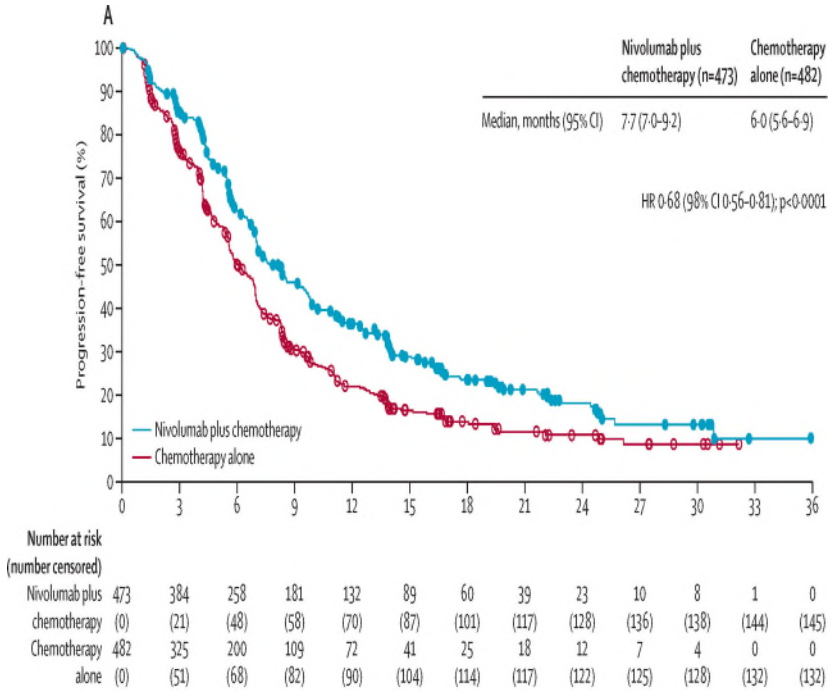




Janjigian Y et al. *The Lancet* 2021 39827-40

FOLFOX/Nivolumab (PFS)





Janjigian Y et al. *The Lancet* 2021 39827-40

NCCN Guidelines

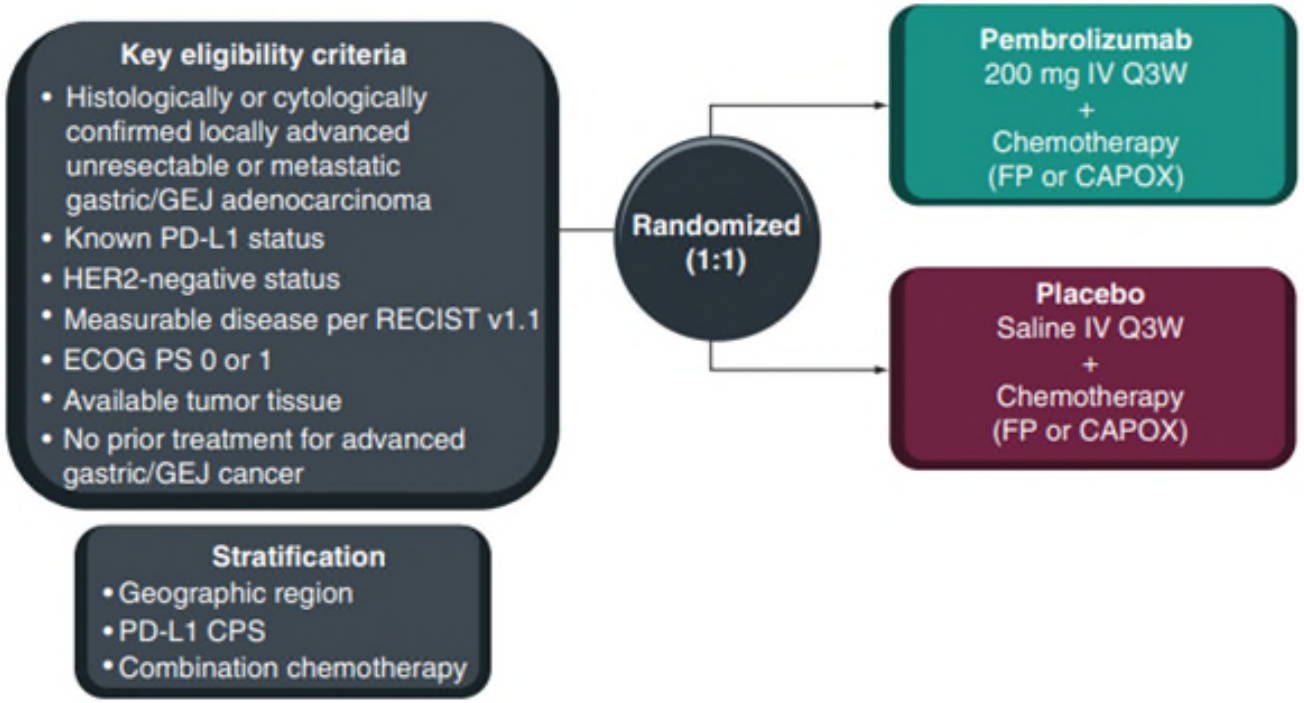
First-Line Therapy
- Oxaliplatin is preferred over cisplatin due to lower toxicity.

Preferred Regimens
- HER2 overexpression positive[d]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and oxaliplatin and trastuzumab[e]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and oxaliplatin and trastuzumab[e] and pembrolizumab[f,g,11]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and cisplatin and trastuzumab (category 1)[e,12]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and cisplatin and trastuzumab[e] and pembrolizumab[f,g,11]
- HER2 overexpression negative[d]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[f,g,13]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and oxaliplatin[14-16]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and cisplatin[14,17-19]

Other Recommended Regimens
- Fluorouracil[a,h] and irinotecan[i,20]
- Paclitaxel with or without carboplatin or cisplatin[i,21-25]
- Docetaxel with or without cisplatin[i,26-29]
- Fluoropyrimidine[i,18,30,31] (fluorouracil[a] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[a,i,32,33]

Useful in Certain Circumstances
- HER2 overexpression negative[d]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS <5) (category 2B)[f,g,13]

KeyNote-589



- Median OS was 12.9 months with pembrolizumab plus chemotherapy vs 11.5 months with chemotherapy
- Median progression-free survival was 6.9 months vs 5.6 months, respectively (HR = 0.76, $P < .0001$).
- Objective responses were achieved by 51.3% of patients on the pembrolizumab arm and 42.0% of the control arm ($P = .00009$). Responses in the pembrolizumab arm were more durable, she said, with median durations of response of 8.0 months vs 5.7 months, respectively.

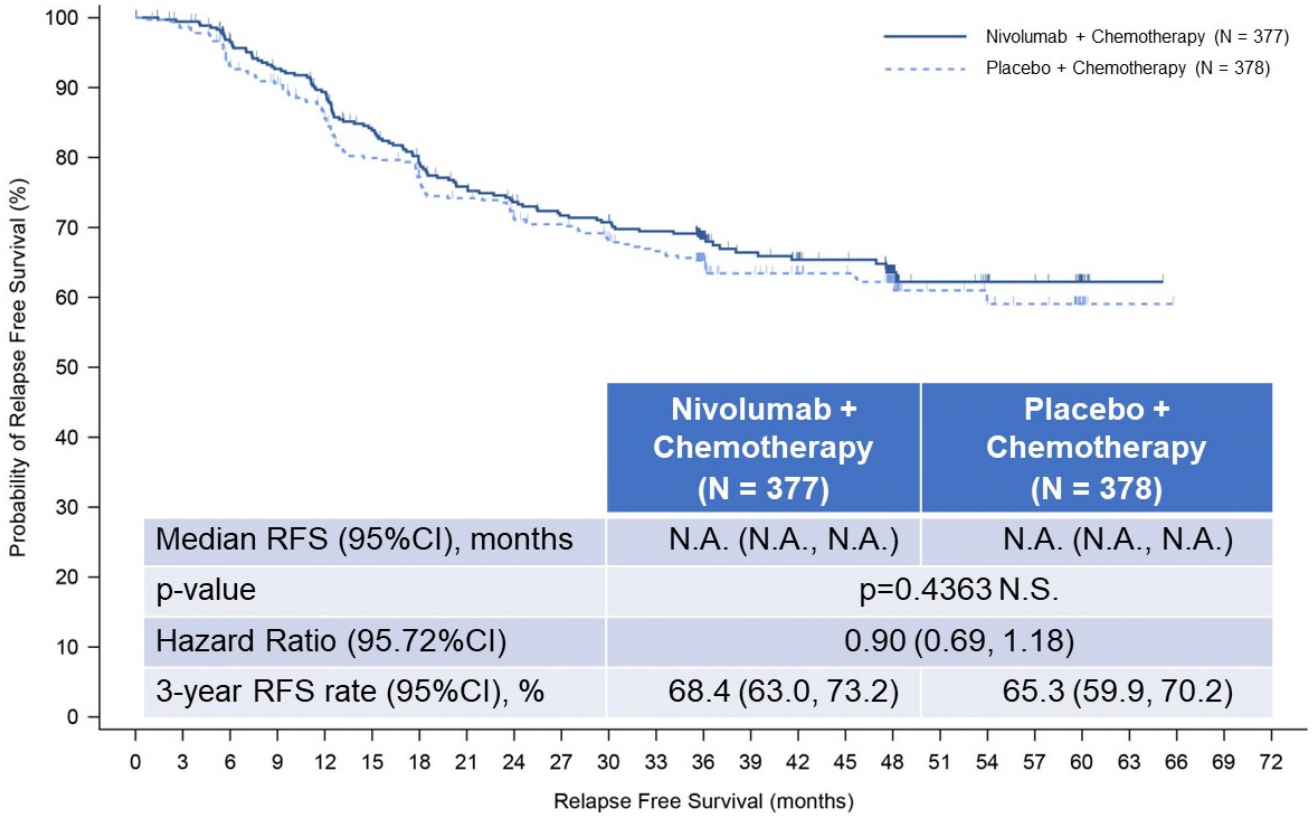
PDL1 Testing

From: Choice of PD-L1 immunohistochemistry assay influences clinical eligibility for gastric cancer immunotherapy

Assay	CPS ≥ 1	CPS ≥ 5	CPS ≥ 10
22C3	170 (49.4%)	46 (13.4%)	24 (7.0%)
28–8	242 (70.3%)	100 (29.1%)	47 (13.7%)
SP-142	170 (49.4%)	68 (19.8%)	33 (9.6%)

Yeong J et al. *Gastric Cancer* volume 25, pages741–750 (2022)

Adjuvant Immunotherapy



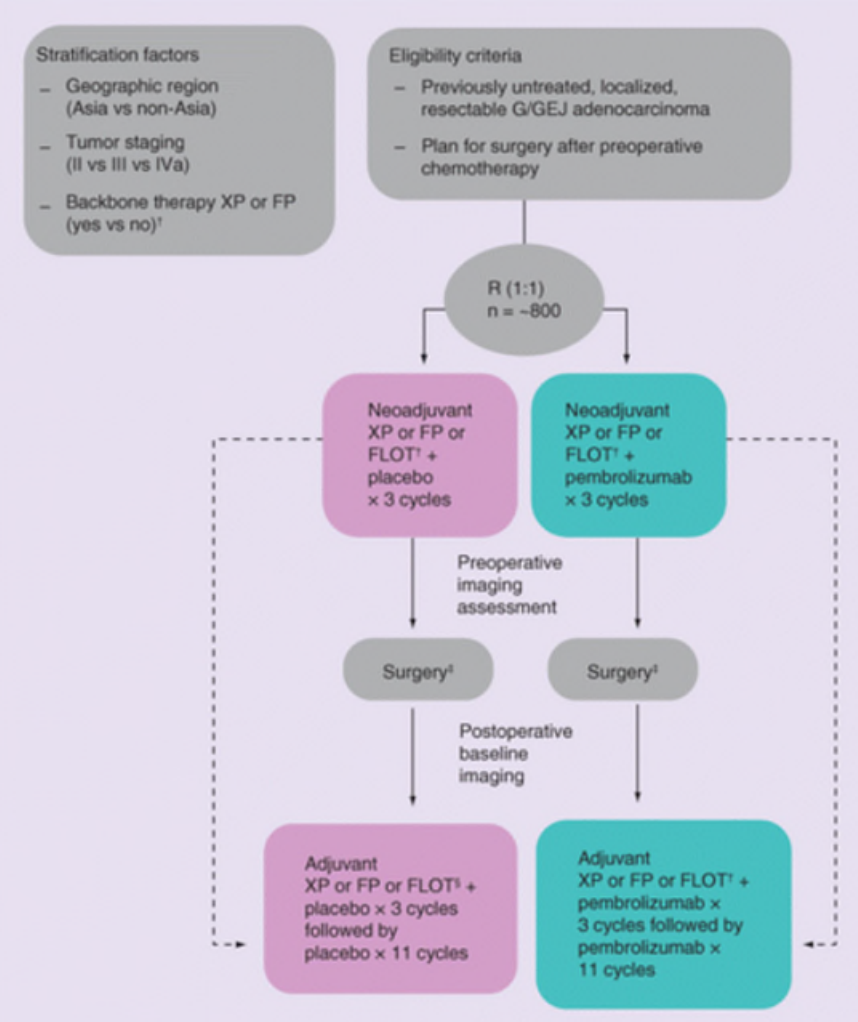
	Nivolumab + Chemotherapy (N = 377)	Placebo + Chemotherapy (N = 378)
Median RFS (95%CI), months	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)
p-value	p=0.4363 N.S.	
Hazard Ratio (95.72%CI)	0.90 (0.69, 1.18)	
3-year RFS rate (95%CI), %	68.4 (63.0, 73.2)	65.3 (59.9, 70.2)

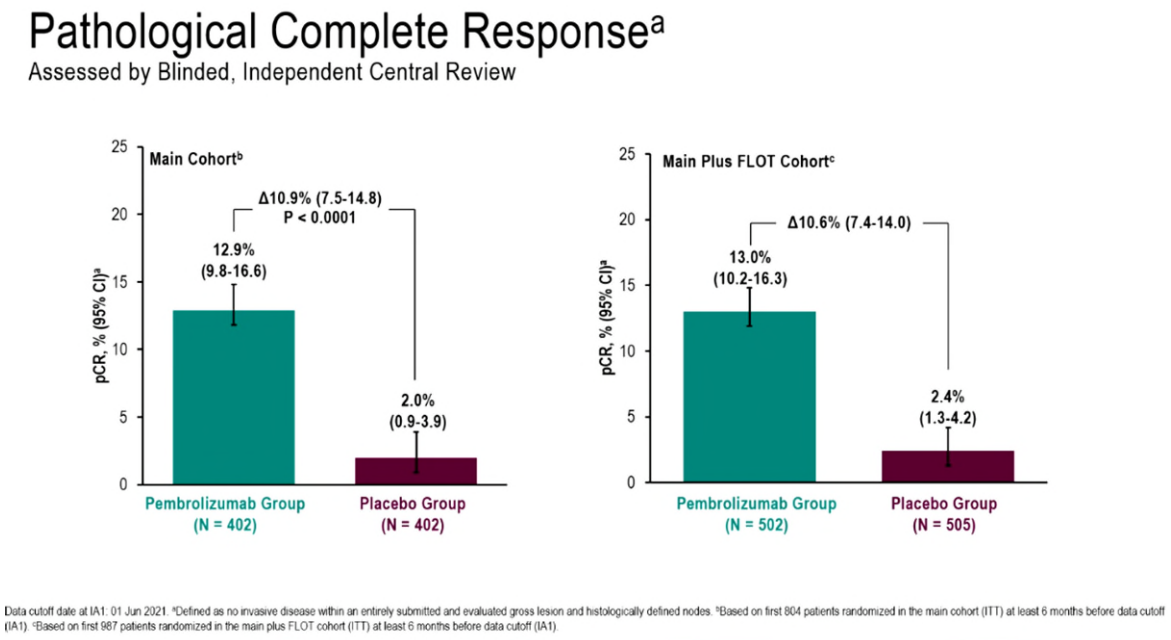
At Risk

Nivolumab + Chemotherapy	377	349	326	310	297	273	255	241	231	223	219	214	162	127	120	114	58	33	28	24	9	1	0	0	0
Placebo + Chemotherapy	378	353	324	311	288	267	254	242	228	223	212	204	148	118	110	107	57	33	30	26	10	1	0	0	0

Perioperative Immunotherapy?

KEYNOTE-585

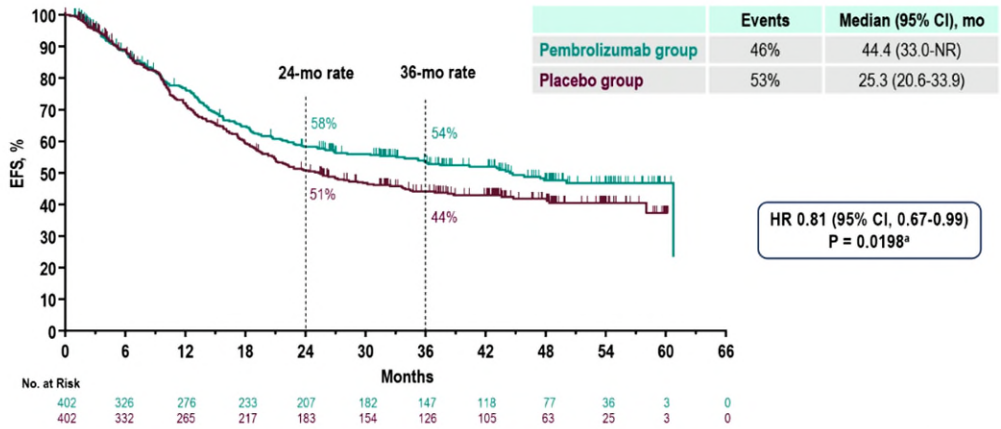




Data cutoff date at IA1: 01 Jun 2021. [a]Defined as no invasive disease within an entirely submitted and evaluated gross lesion and histologically defined nodes. [b]Based on first 804 patients randomized in the main cohort (ITT) at least 6 months before data cutoff (IA1). [c]Based on first 987 patients randomized in the main plus FLOT cohort (ITT) at least 6 months before data cutoff (IA1).

KeyNote-585

Event-Free Survival: Main Cohort

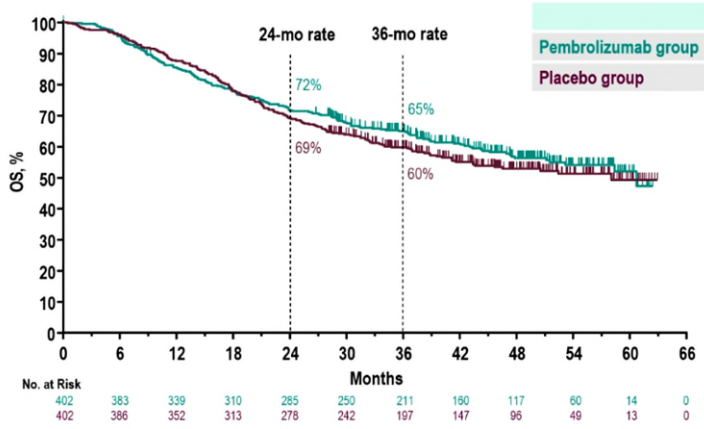


	Events	Median (95% CI), mo
Pembrolizumab group	46%	44.4 (33.0-NR)
Placebo group	53%	25.3 (20.6-33.9)

HR 0.81 (95% CI, 0.67-0.99)
P = 0.0198[a]

Data cutoff date: 09 Feb 2023. [a]Threshold for significance was one-sided P = 0.0178. EFS defined as time from randomization to first occurrence of radiographic disease progression per RECIST v1.1, local or distant recurrence as assesses by CT scan or biopsy if indicated, clinical progression, or death due to any cause per investigator assessment. NR, not reached.

Overall Survival: Main Cohort

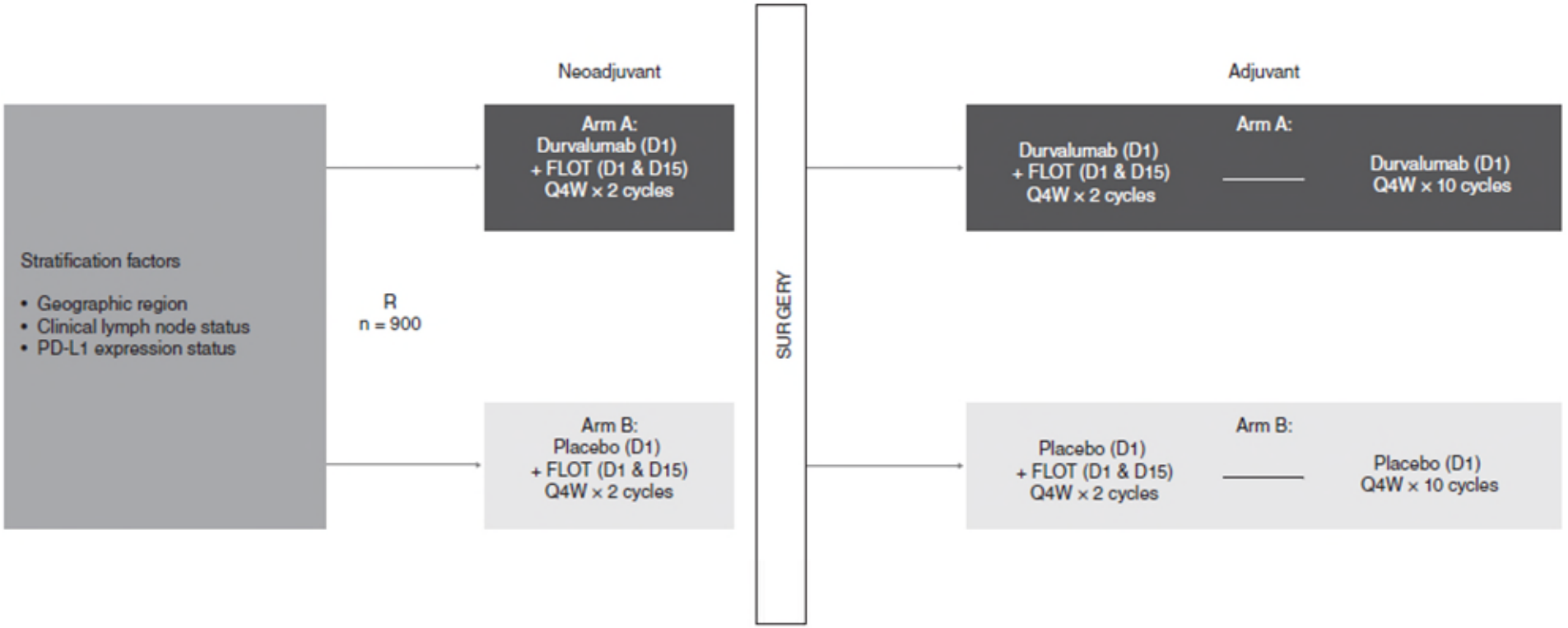


	Events	Median (95% CI), mo
Pembrolizumab group	41%	60.7 (51.5-NR)
Placebo group	45%	58.0 (41.5-NR)

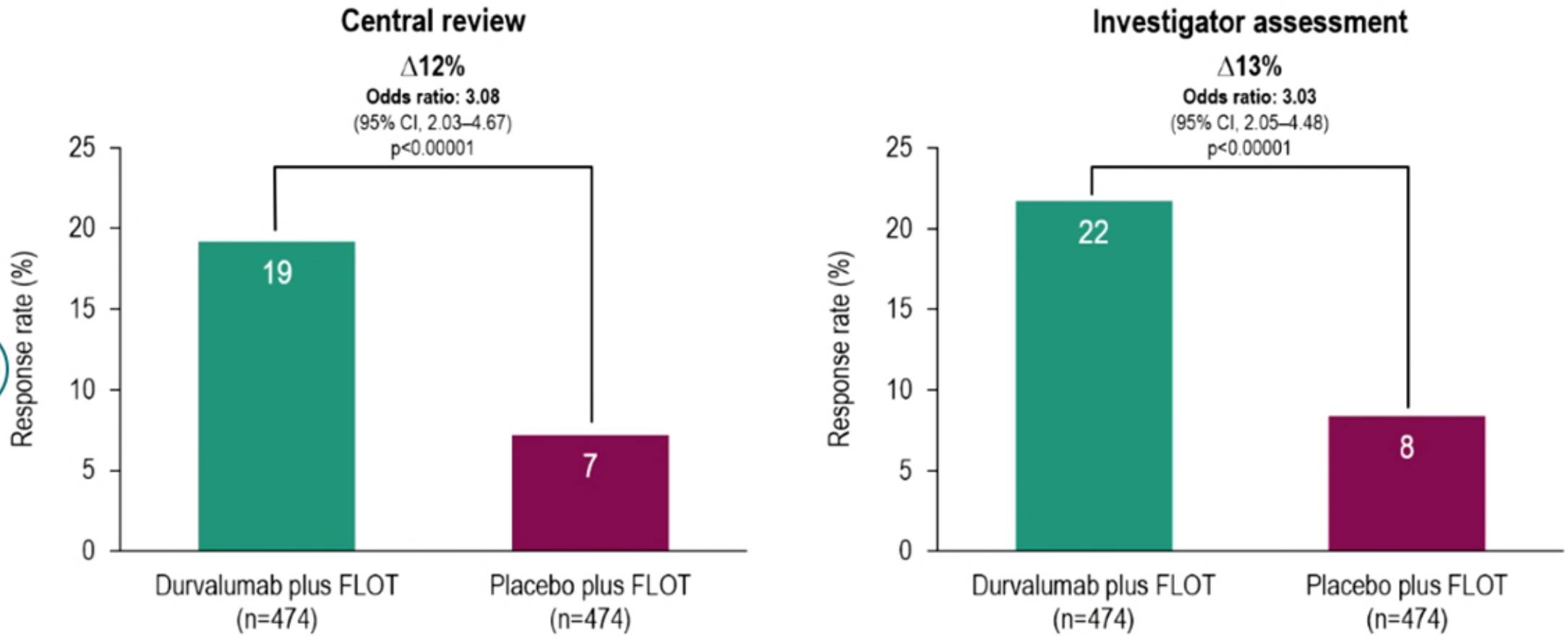
HR 0.90 (95% CI, 0.73-1.12)

Data cutoff date: 09 Feb 2023.

MATTERHORN


Neoadjuvant
Adjuvant
Stratification factors
• Geographic region
• Clinical lymph node status
• PD-L1 expression status
R
n = 900
Arm A:
Durvalumab (D1)
+ FLOT (D1 & D15)
Q4W x 2 cycles
Arm A:
Durvalumab (D1)
+ FLOT (D1 & D15)
Q4W x 2 cycles
Durvalumab (D1)
Q4W x 10 cycles
Arm B:
Placebo (D1)
+ FLOT (D1 & D15)
Q4W x 2 cycles
Arm B:
Placebo (D1)
+ FLOT (D1 & D15)
Q4W x 2 cycles
Placebo (D1)
Q4W x 10 cycles
SURGERY

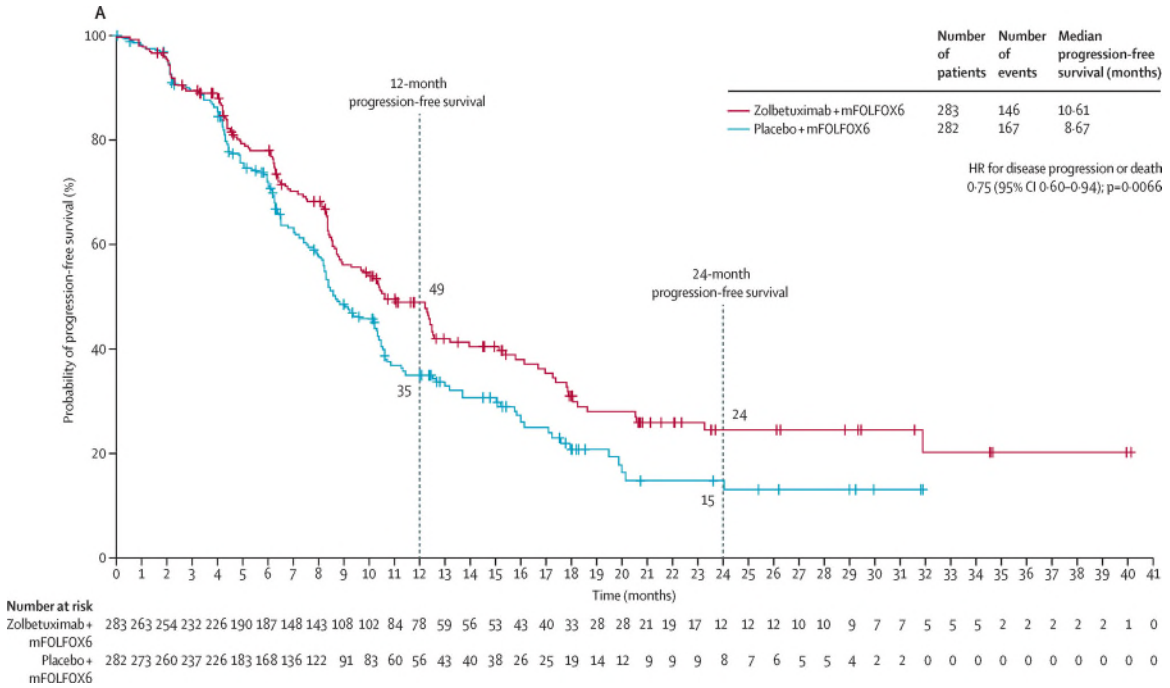
Pathological complete response

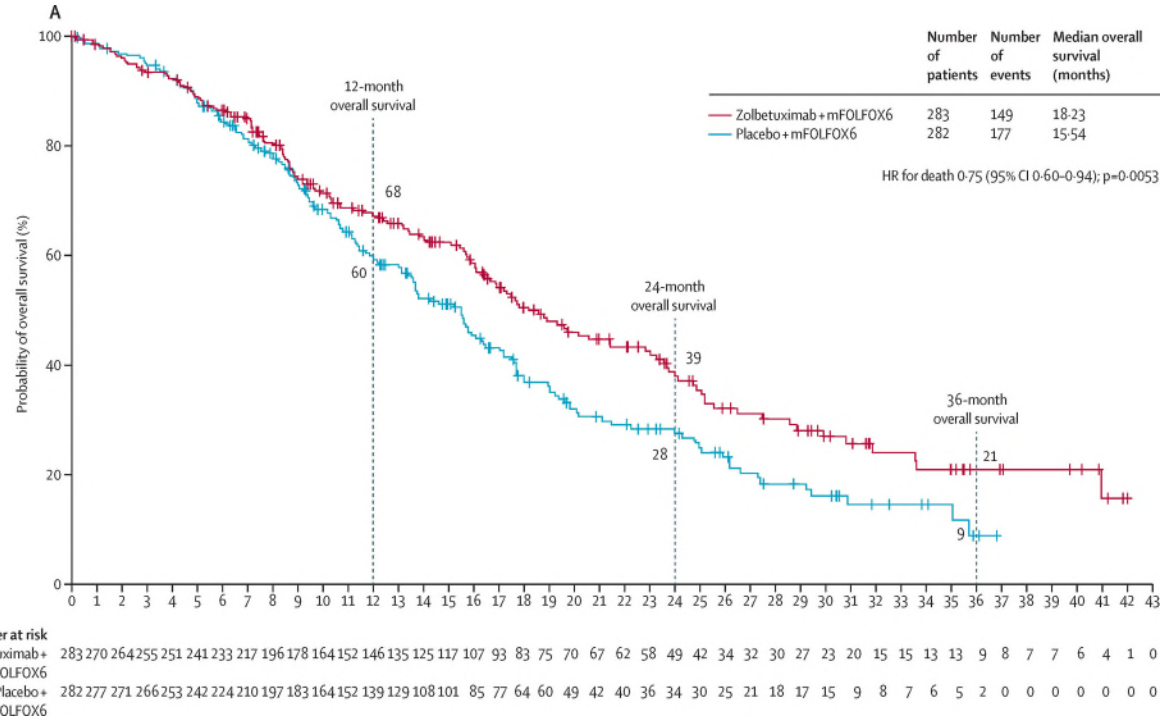


Participants achieve pCR if there is no residual viable tumour cells found at primary tumour and resected lymph nodes at the time of resection, meaning a pathological regression of -100%, based on central (or local) assessment. Central review of pCR was scored using modified Ryan criteria which assess both the primary tumour and lymph nodes.

CI, confidence interval; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; pCR, pathological complete response.

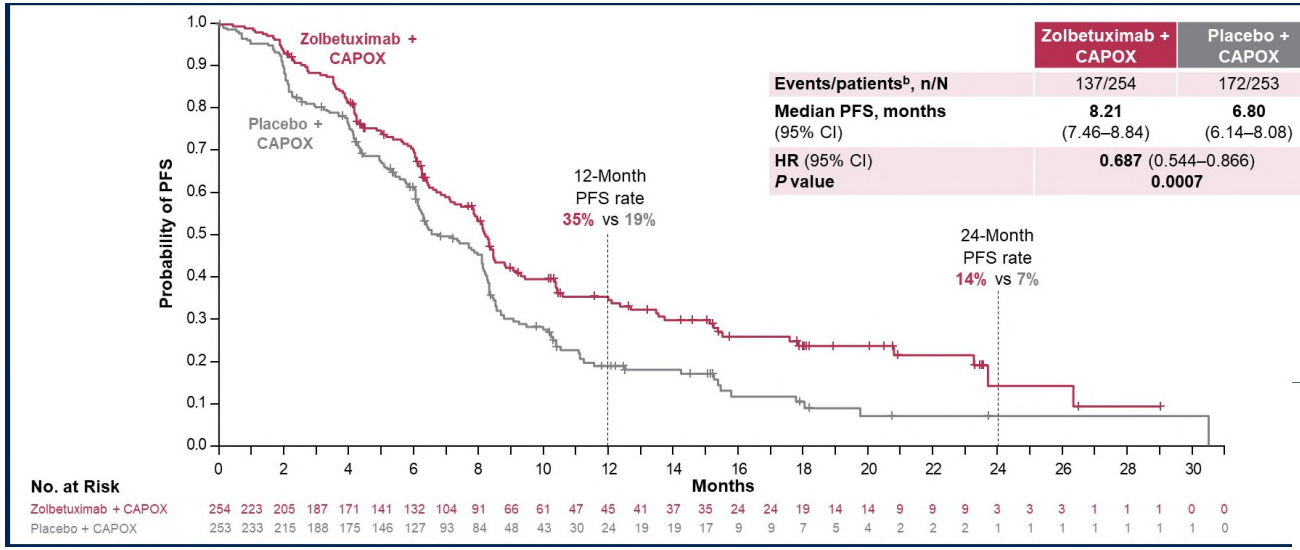
Zolbetuximab (Claudin 18.2)



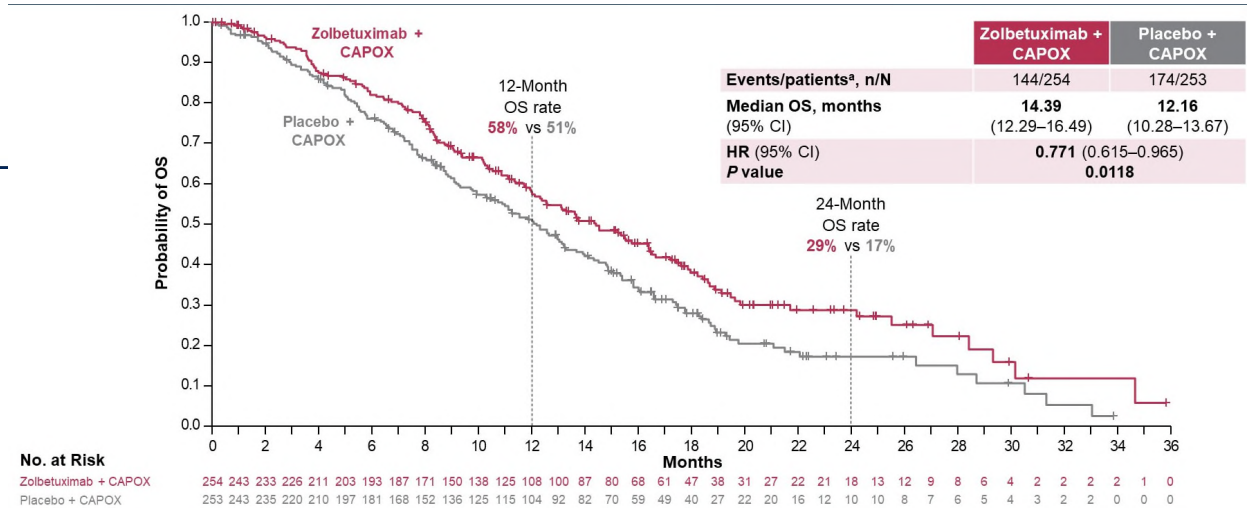


Shitara K et al *The Lancet* 2023 4011655-1668

Zolbetuximab



	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[b], n/N	137/254	172/253
Median PFS, months (95% CI)	**8.21** (7.46–8.84)	**6.80** (6.14–8.08)
HR (95% CI)	**0.687** (0.544–0.866)	
***P* value**	**0.0007**	

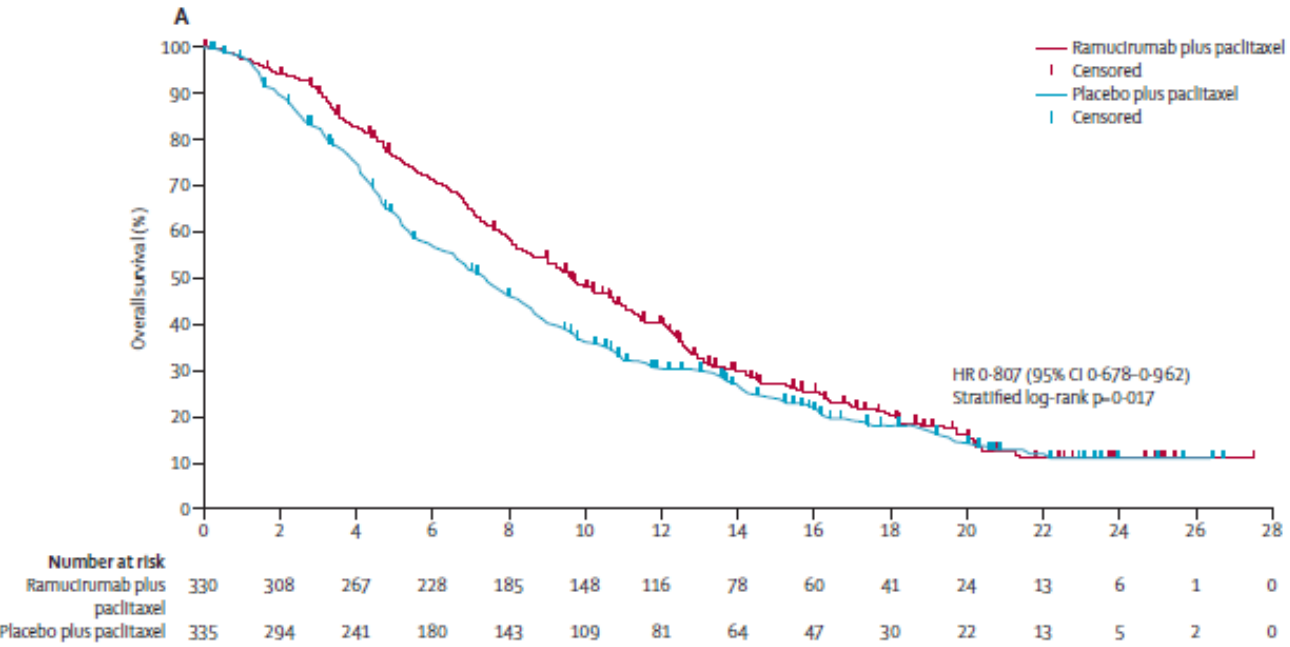


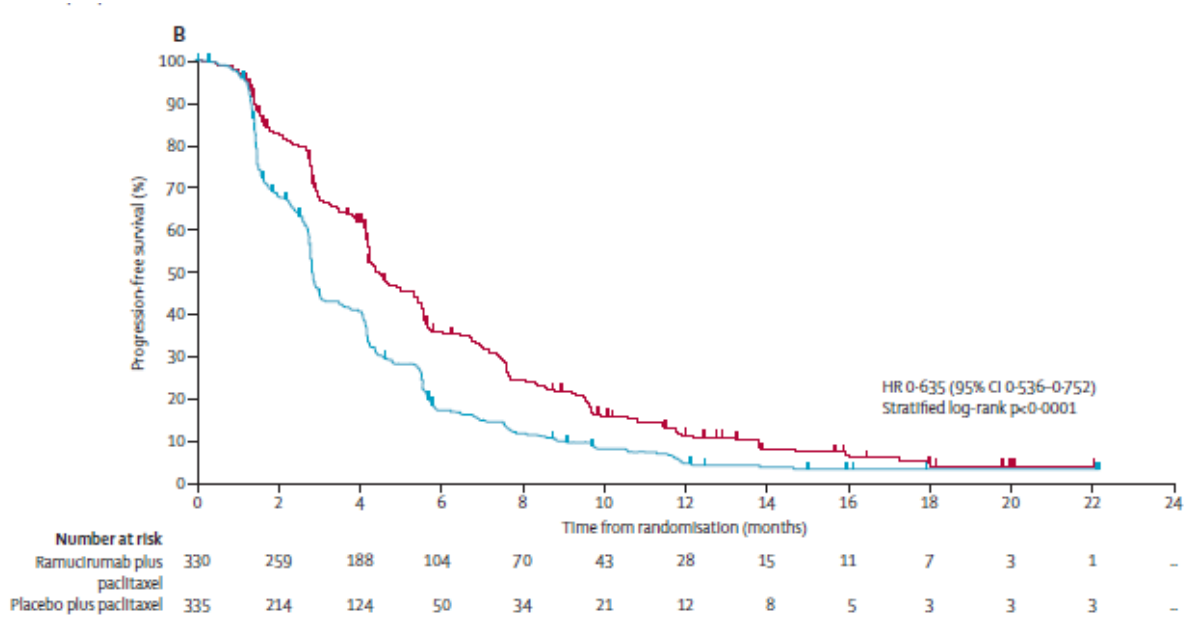
	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[a], n/N	144/254	174/253
Median OS, months (95% CI)	**14.39** (12.29–16.49)	**12.16** (10.28–13.67)
HR (95% CI)	**0.771** (0.615–0.965)	
***P* value**	**0.0118**	

Biomarker Testing

- When to test?
  - At diagnosis of metastatic disease
- How to test?
  - NGS?
  - IHC?
    - What test to use?
  - Both?

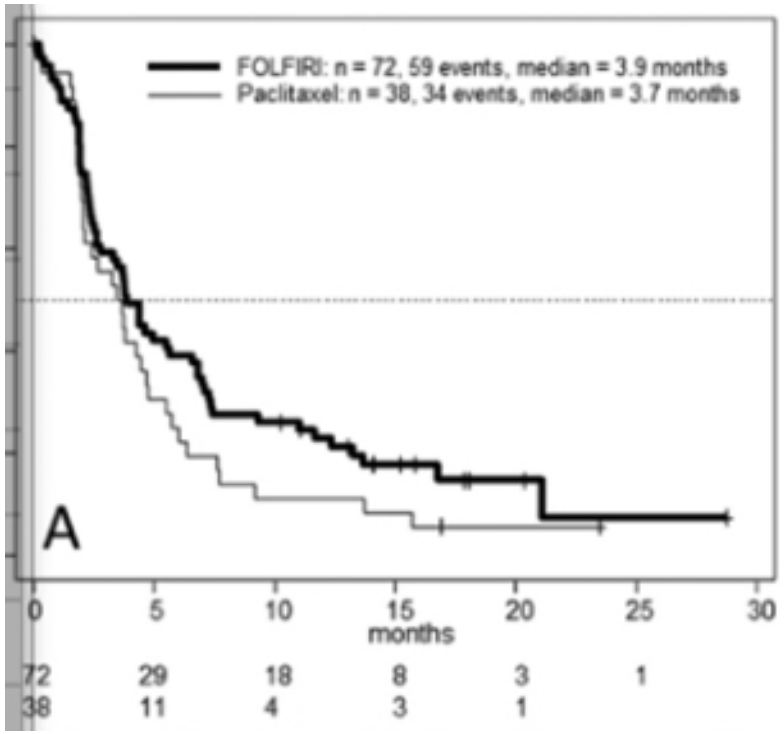
Paclitaxel/Ramucirumab

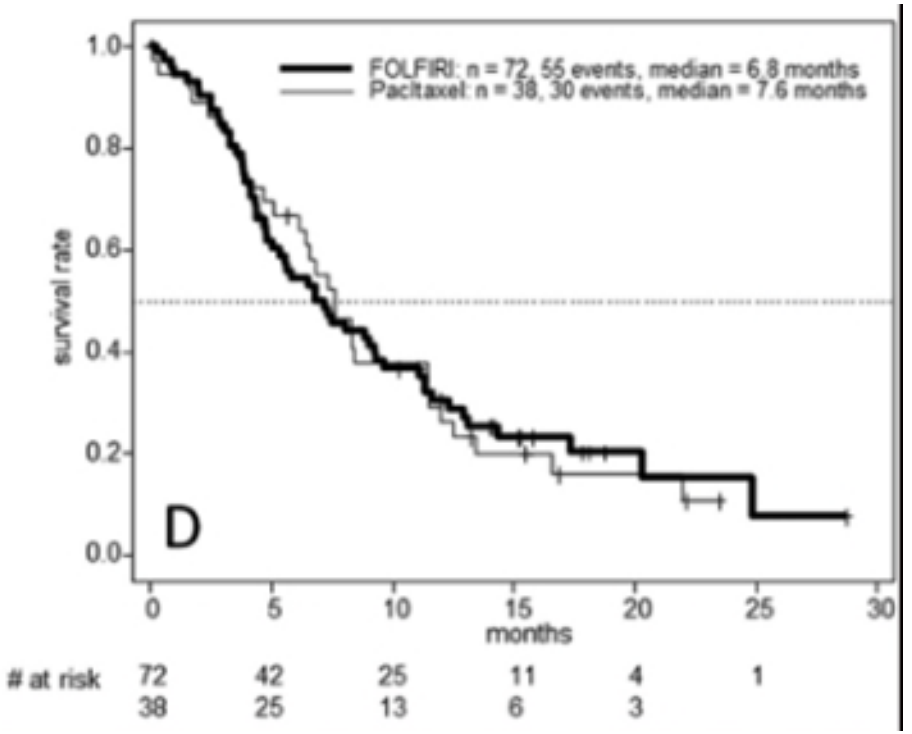




Wilke H et al. Lancet 2014 1224-1235

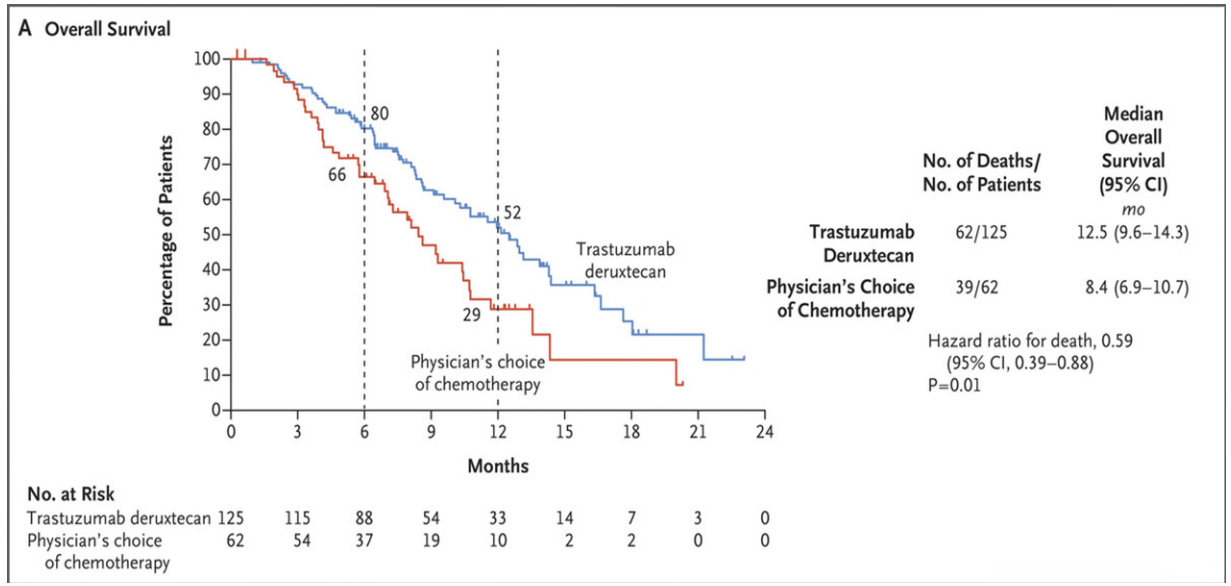
FOLFIRI/Ramucirumab

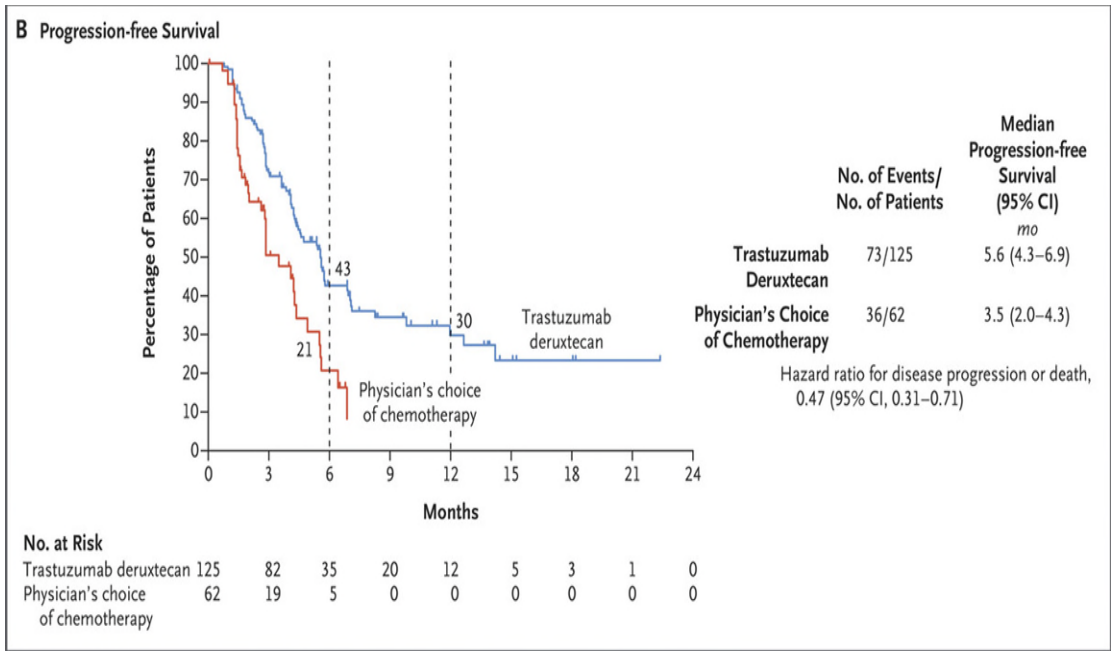




Lorenzen S et al European Journal of Cancer, April 2022, 48-57

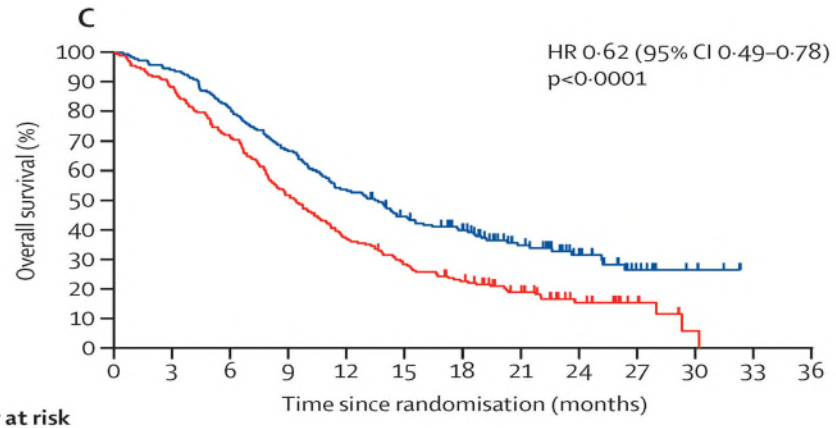
Trastuzumab Deruxtecan



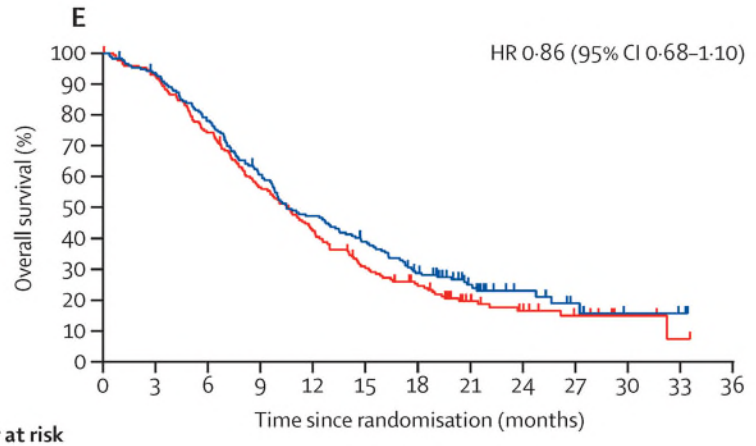


Shitara K et al. N Engl J Med 2020; 2419-2430.

KEYNOTE-590



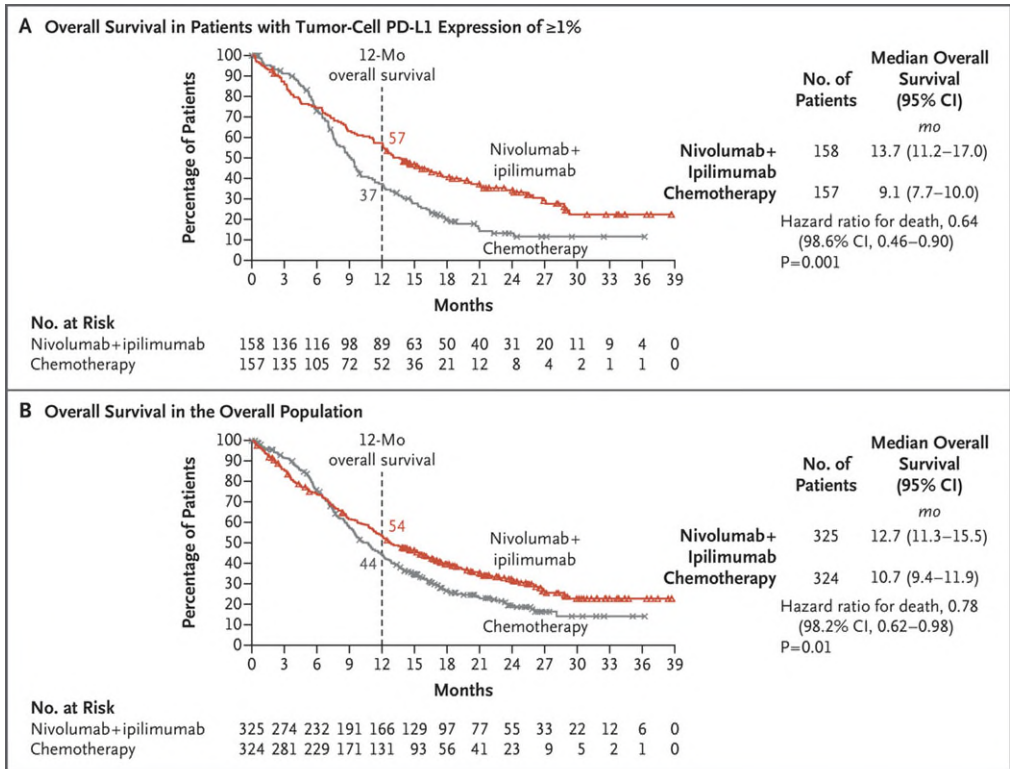
Number at risk (number censored)													
Pembrolizumab plus chemotherapy group	186 (0)	175 (0)	151 (0)	125 (0)	100 (0)	79 (4)	66 (9)	40 (28)	23 (42)	10 (52)	4 (58)	0 (58)	0 (58)
Placebo plus chemotherapy group	197 (0)	174 (0)	142 (0)	102 (0)	73 (0)	55 (1)	42 (3)	28 (11)	13 (22)	6 (29)	1 (32)	0 (32)	0 (32)

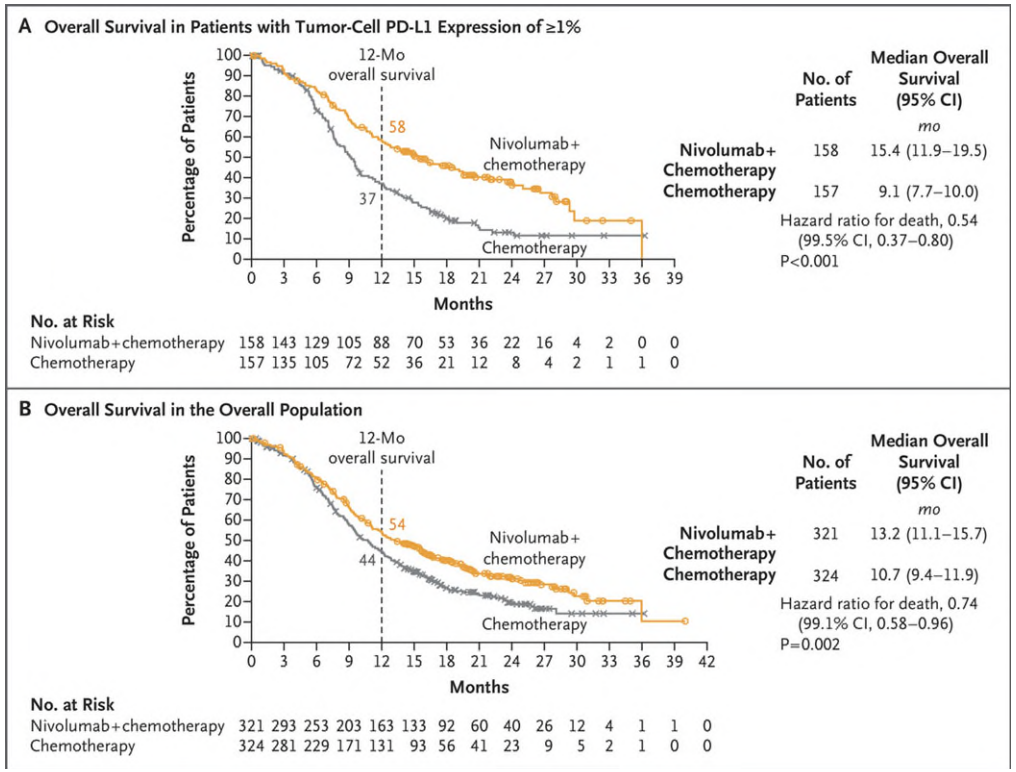


Number at risk (number censored)													
Pembrolizumab plus chemotherapy group	175 (0)	162 (2)	135 (2)	104 (3)	81 (3)	66 (5)	47 (7)	26 (22)	12 (34)	6 (38)	3 (40)	2 (41)	0 (41)
Placebo plus chemotherapy group	172 (0)	159 (1)	127 (1)	96 (2)	72 (2)	51 (4)	38 (8)	21 (17)	14 (21)	9 (25)	3 (31)	1 (32)	0 (32)

Sun JM et al *The Lancet* 2021 398759-771

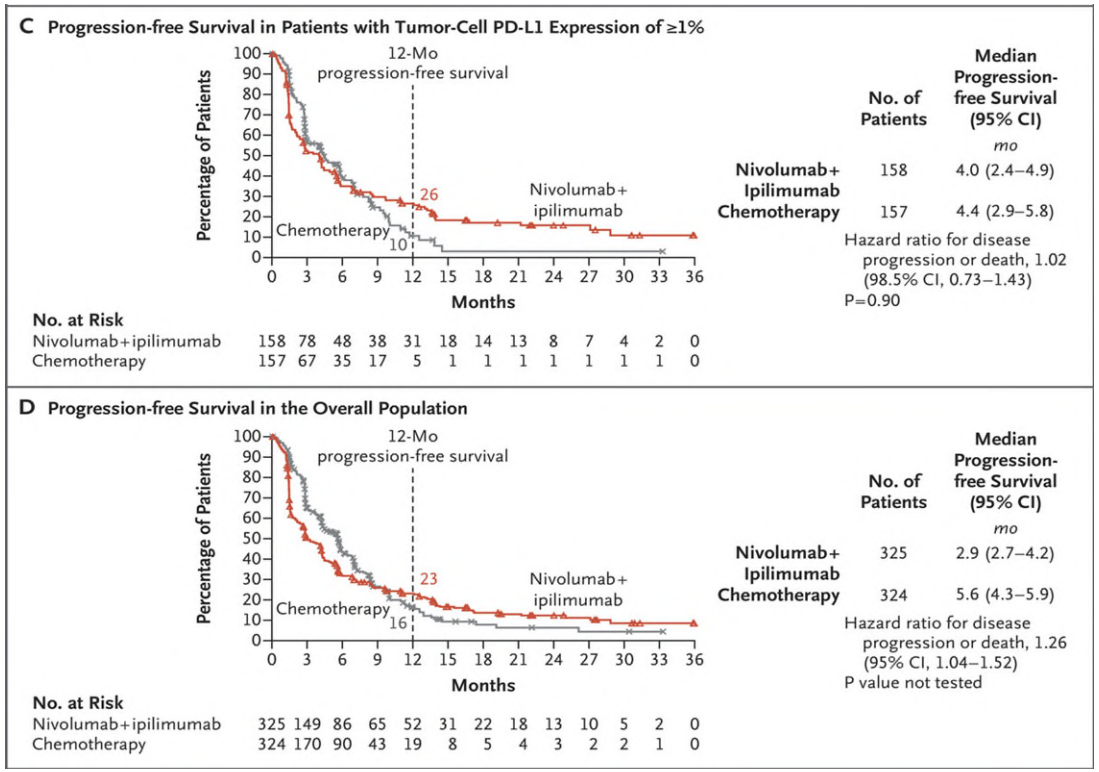
CheckMate-648

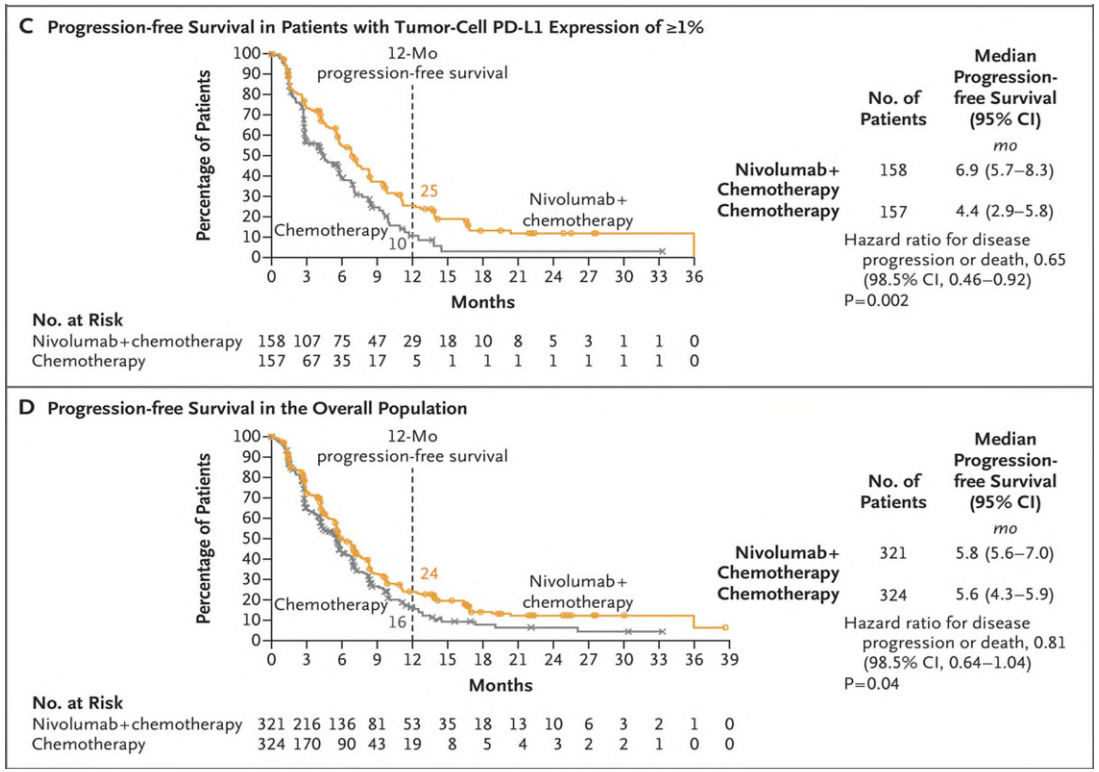




Doki et al. N Engl J Med 2022;386:449-462.

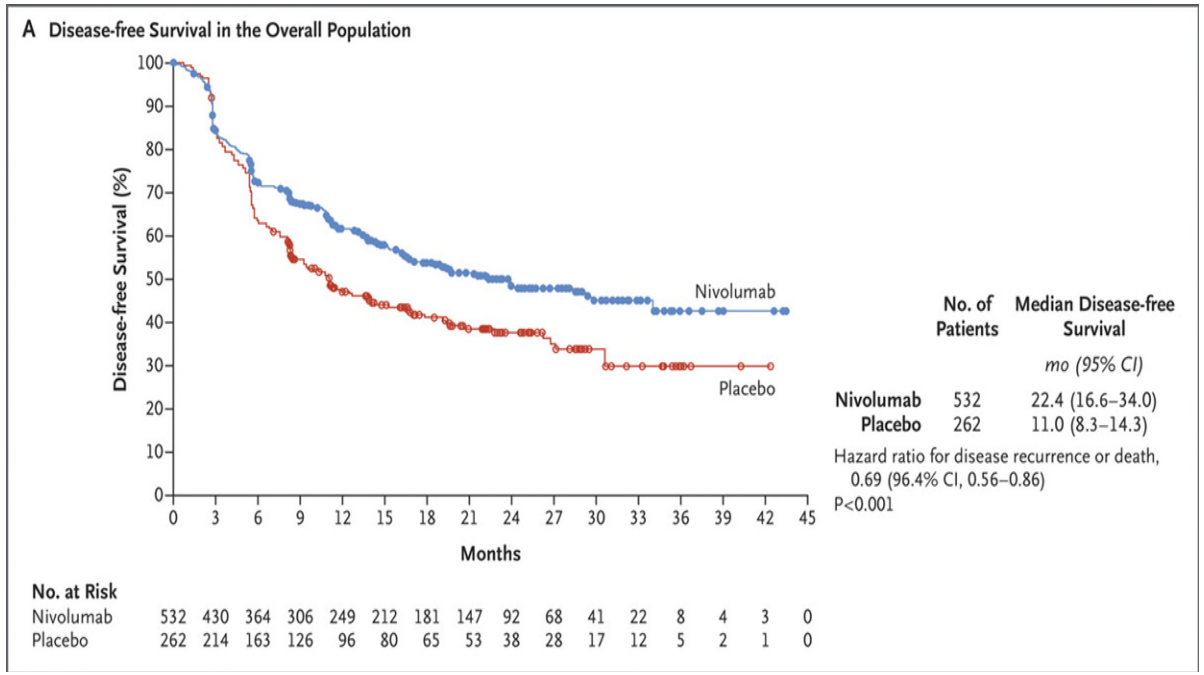
CheckMate-648

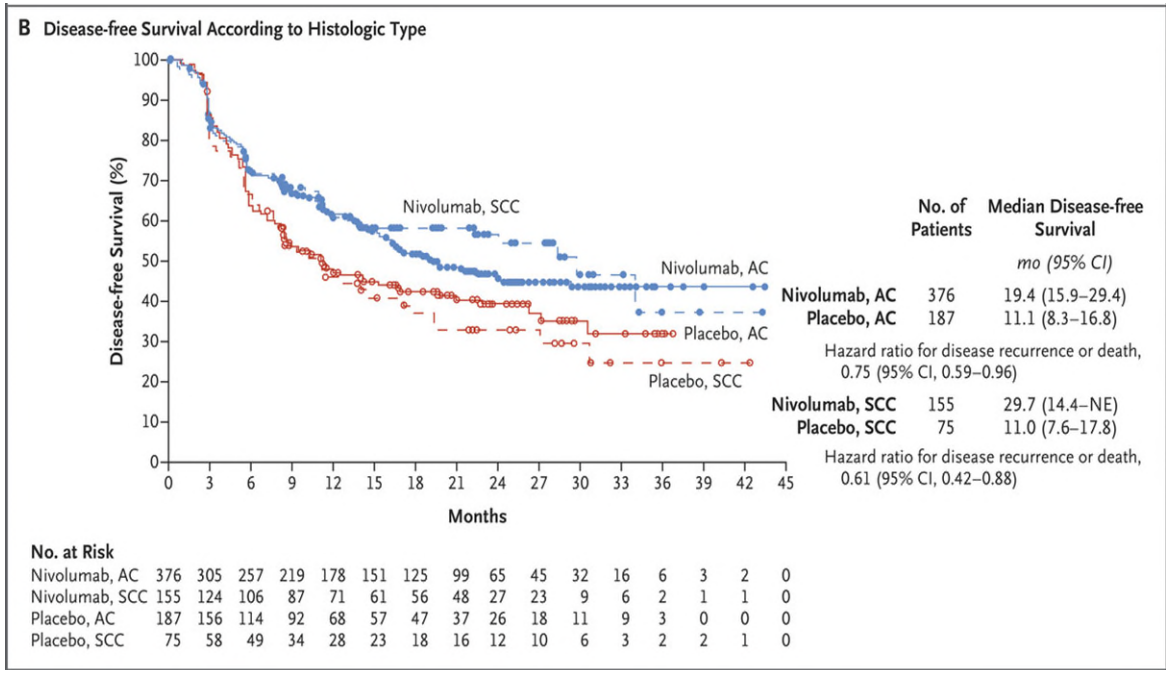




Doki et al. N Engl J Med 2022;386:449-462.

Adjuvant Immunotherapy

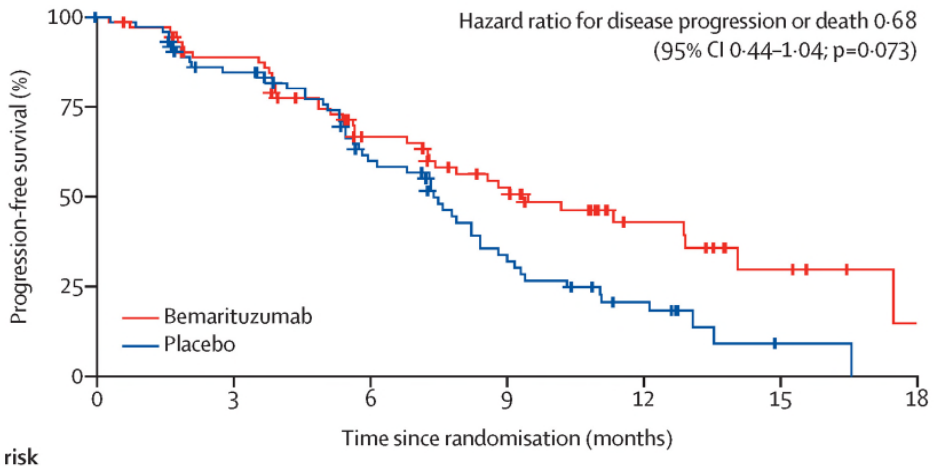




Kelly RJ et al. N Engl J Med 2021

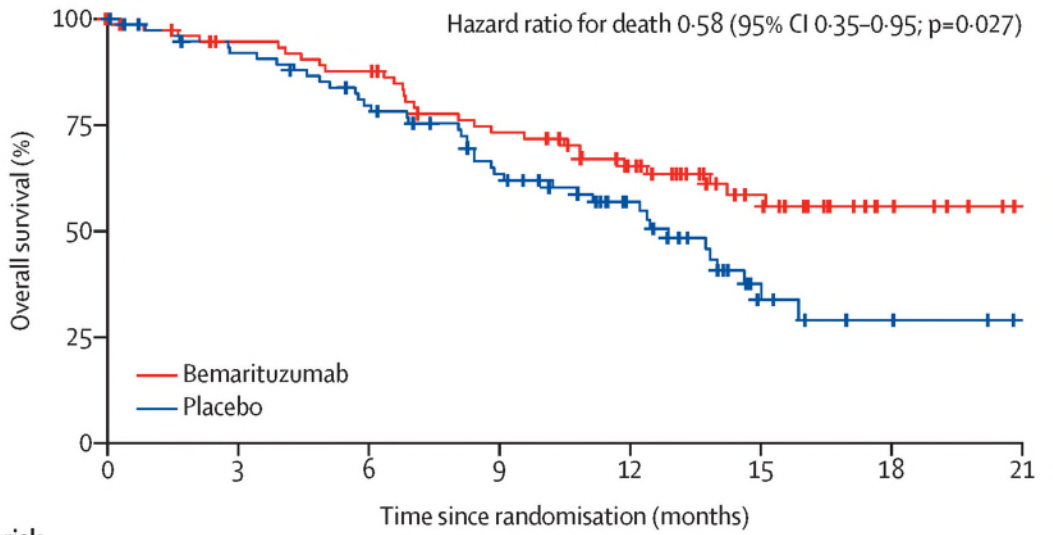
FGFR2 Amplification and overexpression of the FGFR2b splice variant

A



Number at risk (number censored)							
Bemarituzumab	77 (0)	62 (7)	40 (14)	28 (18)	12 (30)	5 (34)	1 (37)
Placebo	78 (0)	59 (8)	37 (14)	19 (17)	9 (20)	1 (25)	0 (25)

A



Number at risk (number censored)								
Bemarituzumab	77 (0)	68 (5)	63 (5)	50 (8)	38 (15)	21 (29)	6 (43)	0 (49)
Placebo	78 (0)	68 (4)	57 (6)	42 (10)	27 (21)	10 (30)	4 (34)	1 (37)

Wainberg Z et al. *The Lancet Oncology* 2022 231430-1440

Conclusions

- The options for treatment of patients with esophagogastric cancers is increasing rapidly
- Biomarker testing, and test interpretation remains crucial in delivery of appropriate care
- Some treatments are specific to the tumor location and histology and not generalizable to all

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

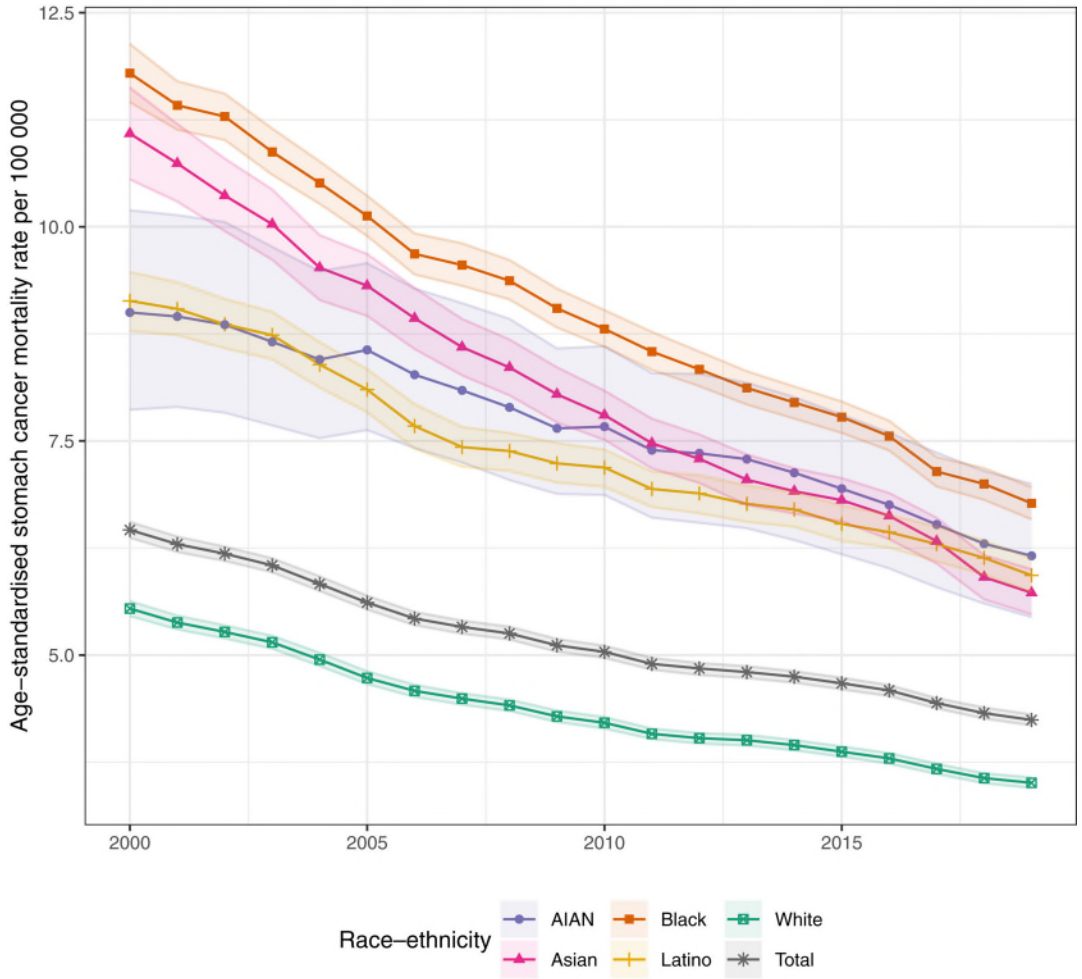
EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- Young adults have a special need for attention to fertility issues and certain survivorship issues are more relevant to this population.
- Lack of personalization of care to the needs of this population.

Age Standardized Mortality



Kendrick P, at al. The Lancet Regional Health – Americas 2023