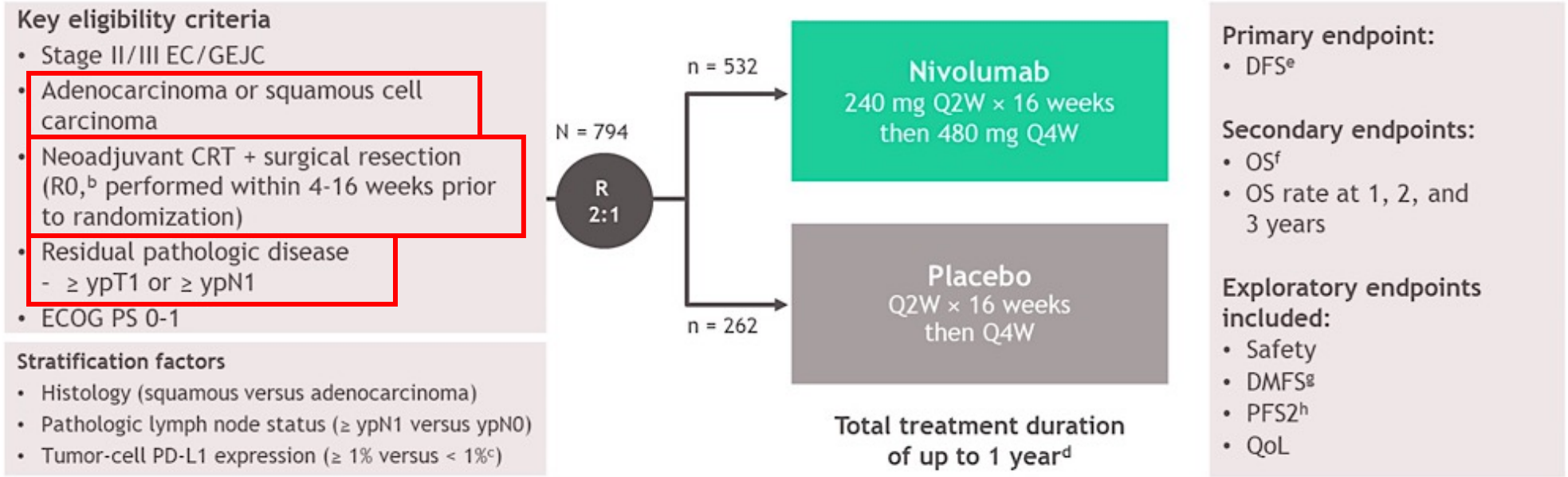
MODULE 2: Gastrointestinal Cancers

Rutika Mehta, MD, MPH
Associate Member in the Department
of Gastrointestinal Oncology
Moffitt Cancer Center
Associate Professor in the Department
of Oncologic Sciences
University of South Florida
Tampa, Florida

Adjuvant treatment after neoadjuvant chemoradiation

CheckMate 577, a global, randomized, double-blind, placebo-controlled phase 3 trial to evaluate a checkpoint inhibitor as adjuvant therapy in patients with esophageal or gastroesophageal junction cancer.

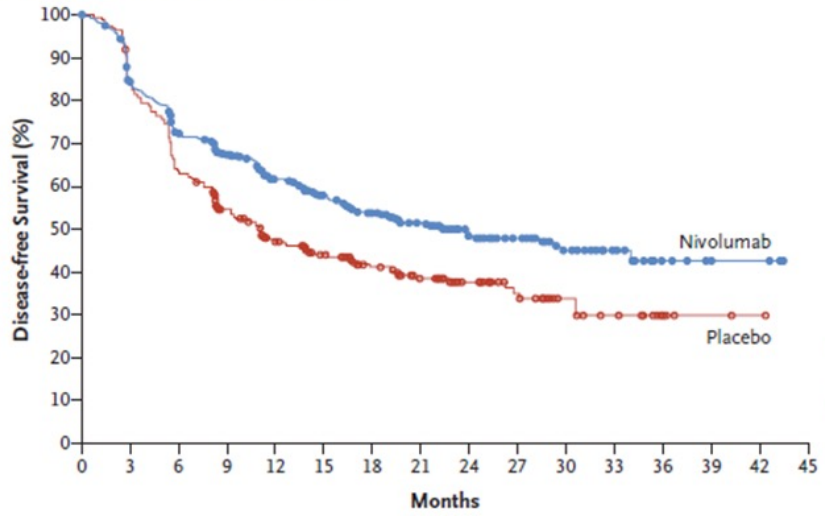


- Median follow-up was 24.4 months (range, 6.2-44.9)[i]
- Geographical regions: Europe (38%), United States and Canada (32%), Asia (13%), rest of the world (16%)

Kelly et al. JCO 2021. Kelly et al. NEJM. 2021

Adjuvant nivolumab- New standard of care

A Disease-free Survival in the Overall Population

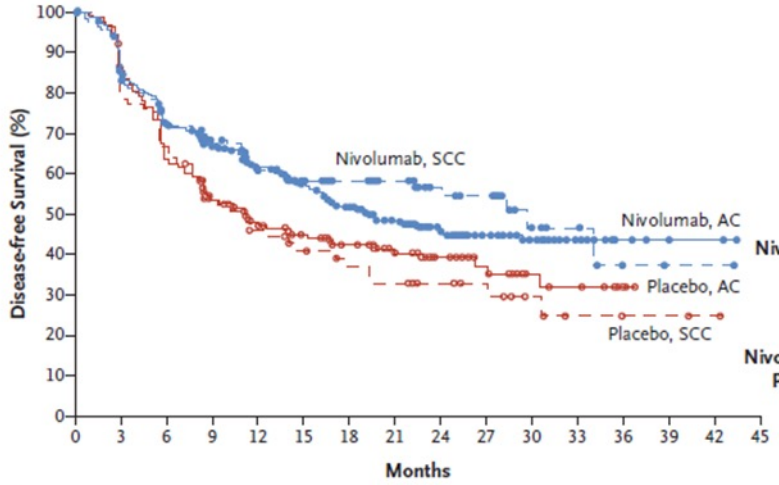


No. at Risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

	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

B Disease-free Survival According to Histologic Type



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

	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)

Discussion Question

Which patients with localized gastroesophageal cancer should be offered adjuvant nivolumab?

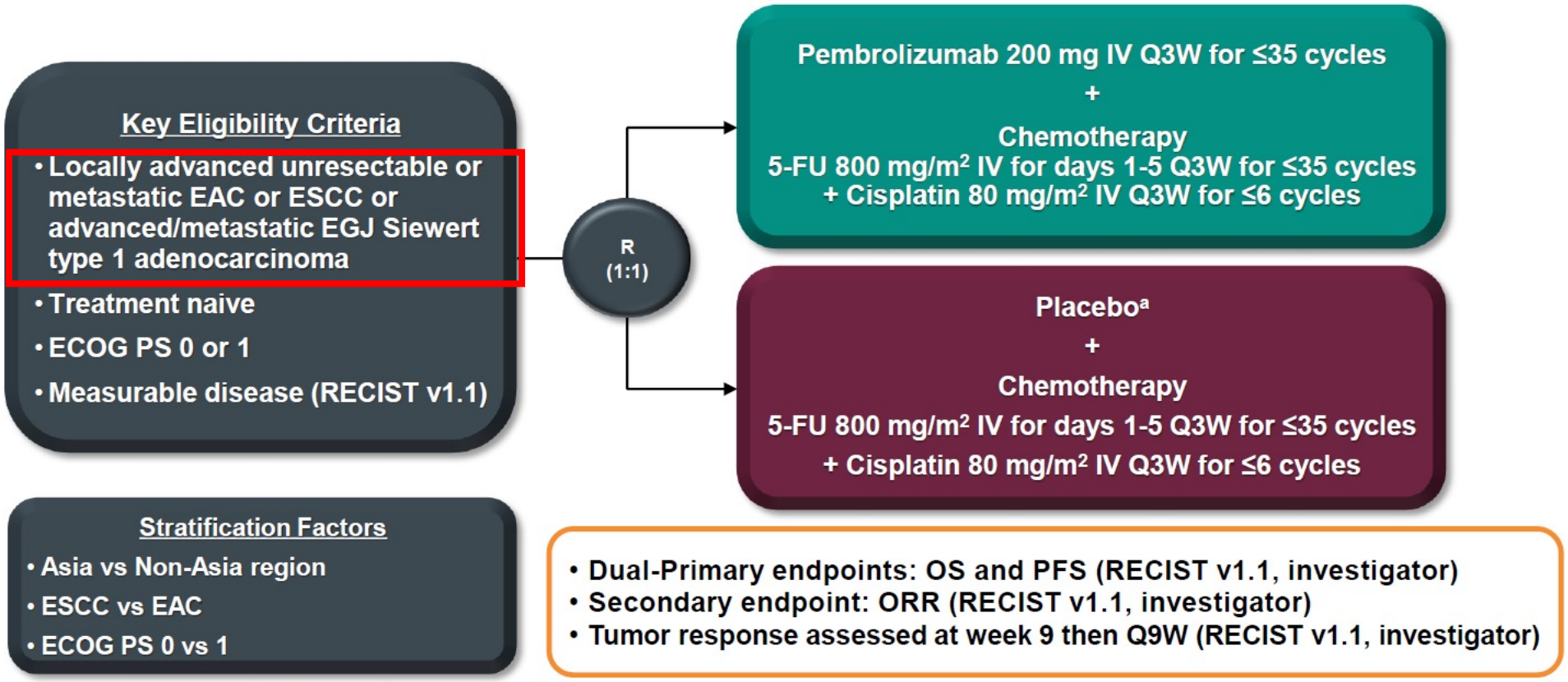
RTP
RESEARCH
TO PRACTICE

Question 1

Which patients with localized gastroesophageal cancer should be offered treatment with adjuvant nivolumab?

Patients with Stage II/III locally advanced esophageal or GEJ cancer who have received chemoradiation and surgery, undergone R0 resection with residual disease are eligible to receive adjuvant nivolumab.

KEYNOTE-590 (Esophageal and GEJ Siewert 1)

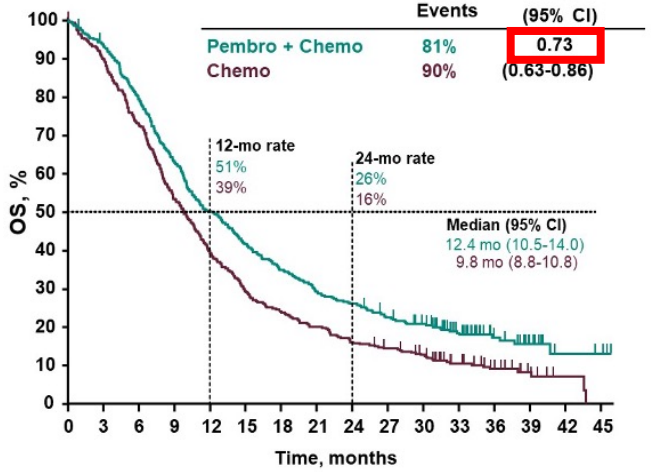


70% ESCC; 50% PD-L1 CPS ≥ 10

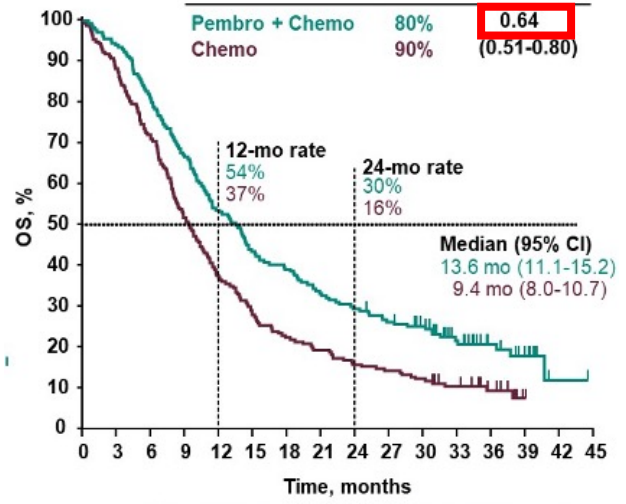
Sun JM et al. Lancet 2021.

KEYNOTE-590 (Esophageal and GEJ Siewert 1)

ALL RANDOMIZED PATIENTS



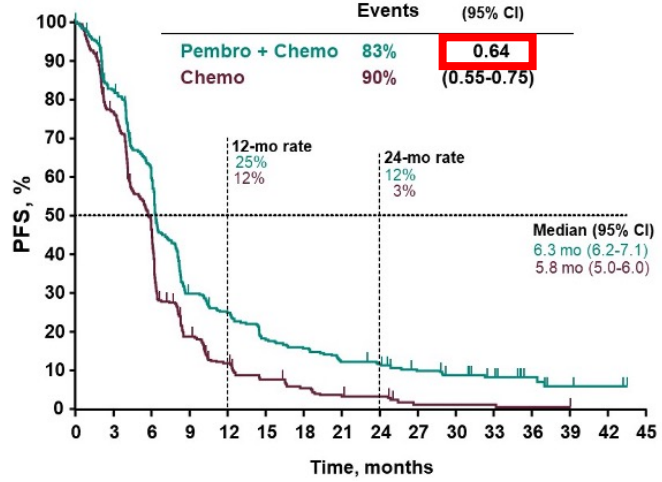
PD-L1 CPS ≥ 10



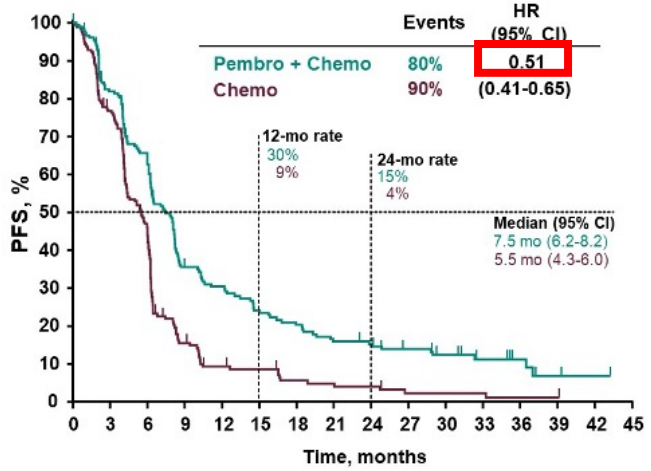
OVERALL SURVIVAL

PROGRESSION FREE SURVIVAL

ALL RANDOMIZED PATIENTS



PD-L1 CPS ≥ 10



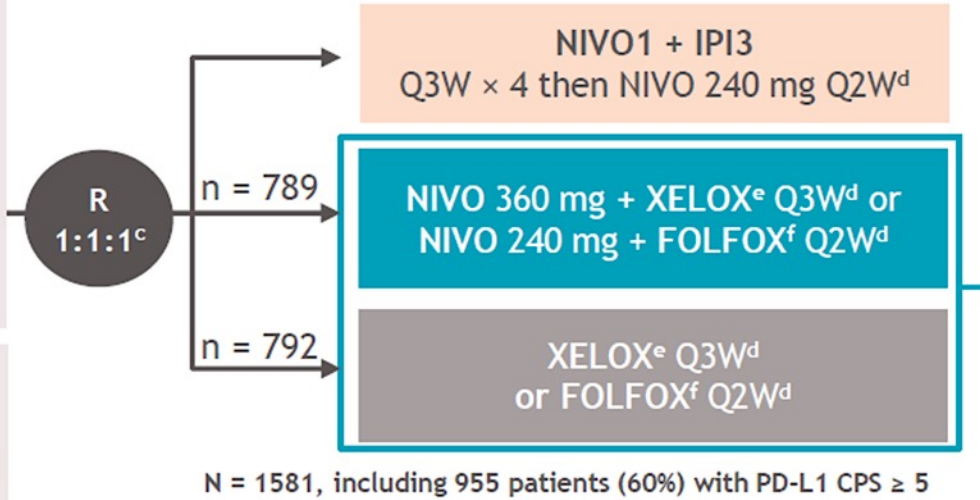
Metges JP et al. Gastrointestinal Cancers Symposium 2022;Abstract 241.

CheckMate 649 (Esophageal/GEJ/Gastric AC)

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

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

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



Dual primary endpoints:
- OS and PFS[g] (PD-L1 CPS ≥ 5)

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

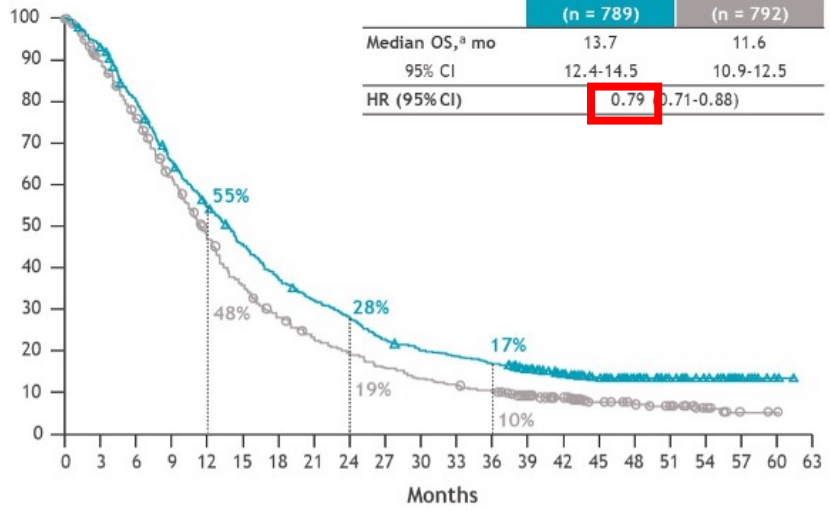
70%- GASTRIC; 16-17%- GEJ; 13-14%- EAC

Janjigian Y. The Lancet 2021.

CheckMate 649 (Esophageal/GEJ/Gastric AC)

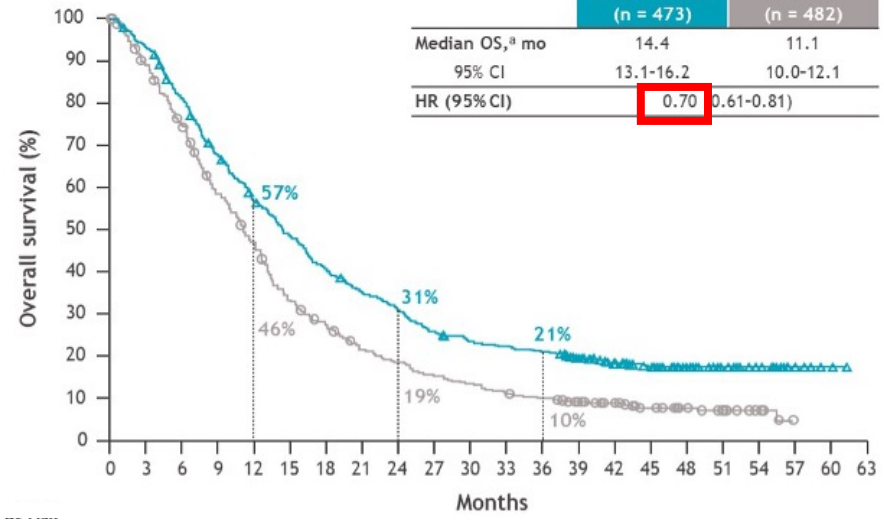
ALL RANDOMIZED PATIENTS

	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS,[a] mo	13.7	11.6
95% CI	12.4-14.5	10.9-12.5
HR (95% CI)	0.79 (0.71-0.88)	



PD-L1 CPS ≥5

	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS,[a] mo	14.4	11.1
95% CI	13.1-16.2	10.0-12.1
HR (95% CI)	0.70 (0.61-0.81)	

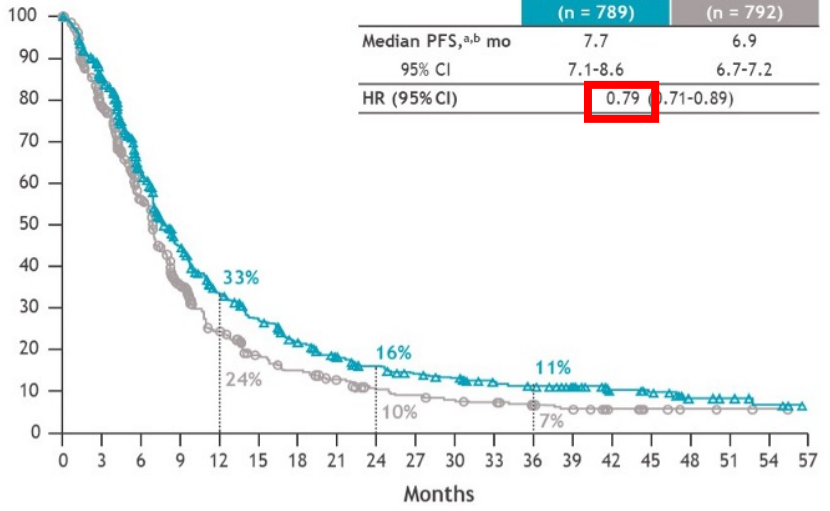


OVERALL SURVIVAL

PROGRESSION FREE SURVIVAL

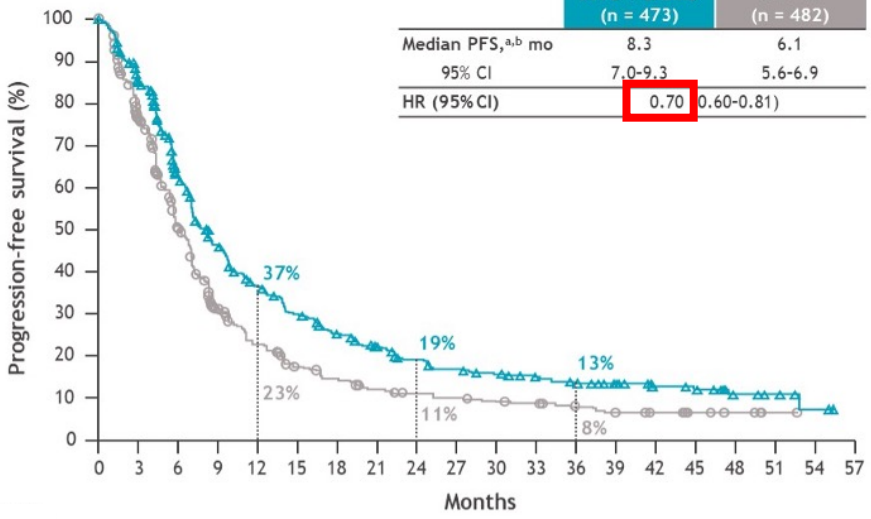
ALL RANDOMIZED PATIENTS

	NIVO + chemo (n = 789)	Chemo (n = 792)
Median PFS,[a,b] mo	7.7	6.9
95% CI	7.1-8.6	6.7-7.2
HR (95% CI)	0.79 (0.71-0.89)	



PD-L1 CPS ≥5

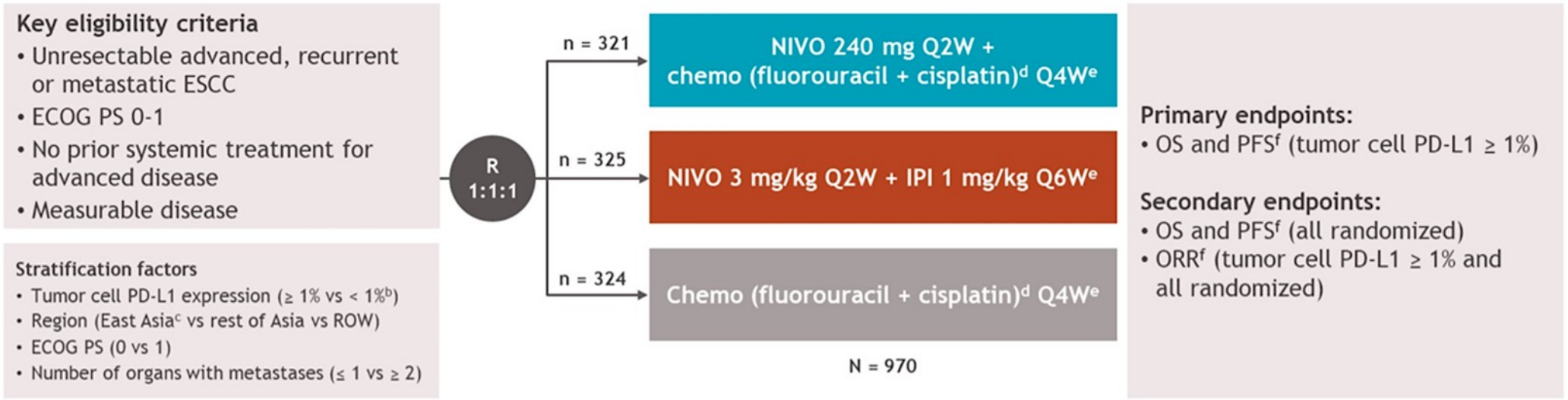
	NIVO + chemo (n = 473)	Chemo (n = 482)
Median PFS,[a,b] mo	8.3	6.1
95% CI	7.0-9.3	5.6-6.9
HR (95% CI)	0.70 (0.60-0.81)	



Janjigian YY. GI ASCO 2023 abst 291.

CheckMate 648 (Esophageal SCC)

- CheckMate 648 is a global, randomized, open-label phase 3 study[a]



- At data cutoff (May 17, 2022), the minimum follow-up[g] was 28.8 months

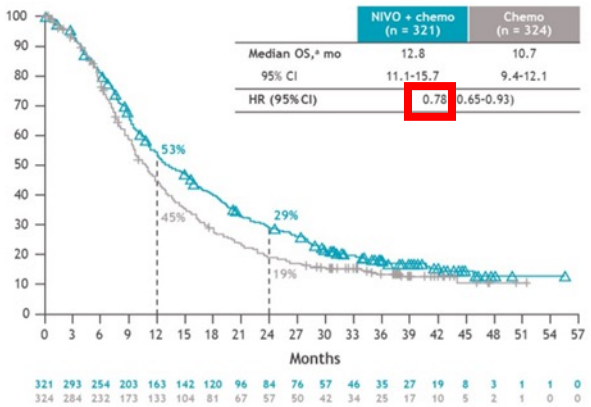
PD-L1 CPS ≥ 1: 91%

Kato K et al. GI ASCO 2023 abst 290

CheckMate 648 (Esophageal SCC)

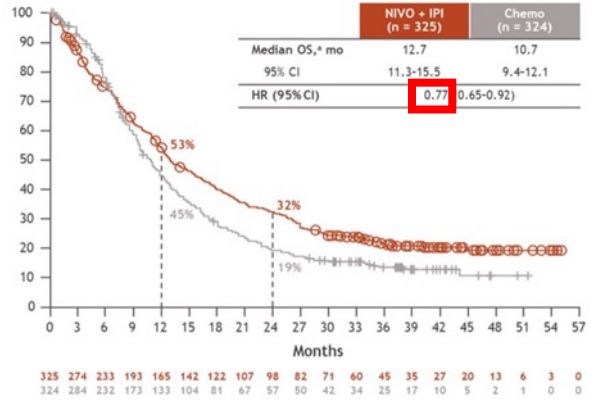
CHEMO+NIVO VS CHEMO

All randomized



IPI+NIVO VS CHEMO

All randomized

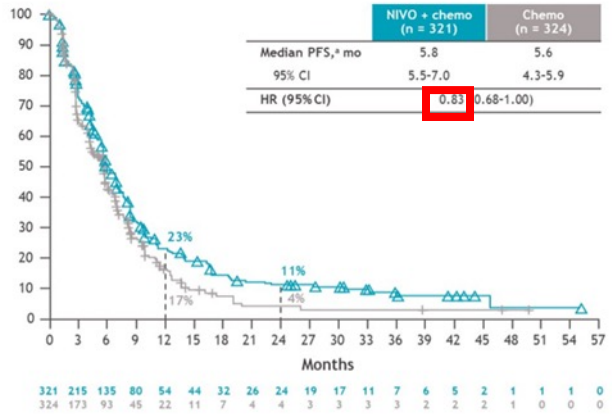


OVERALL SURVIVAL

PROGRESSION FREE SURVIVAL

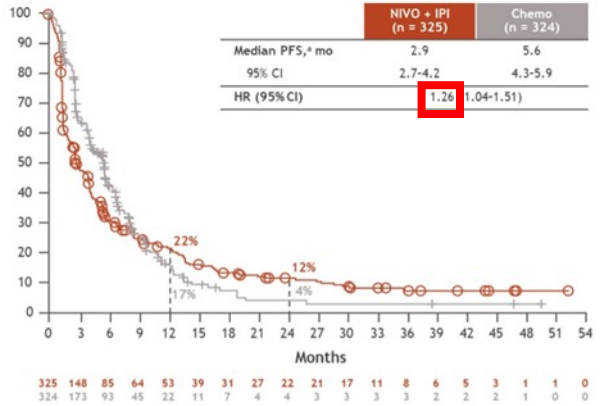
CHEMO+NIVO VS CHEMO

All randomized (per BICR)



IPI+NIVO VS CHEMO

All randomized (per BICR)



Kato K et al. GI ASCO 2023 abst 290

Discussion Question

What is your usual first-line therapy for metastatic HER2-negative gastroesophageal cancer, and how do PD-L1 status, tumor location and histology factor into your decision?

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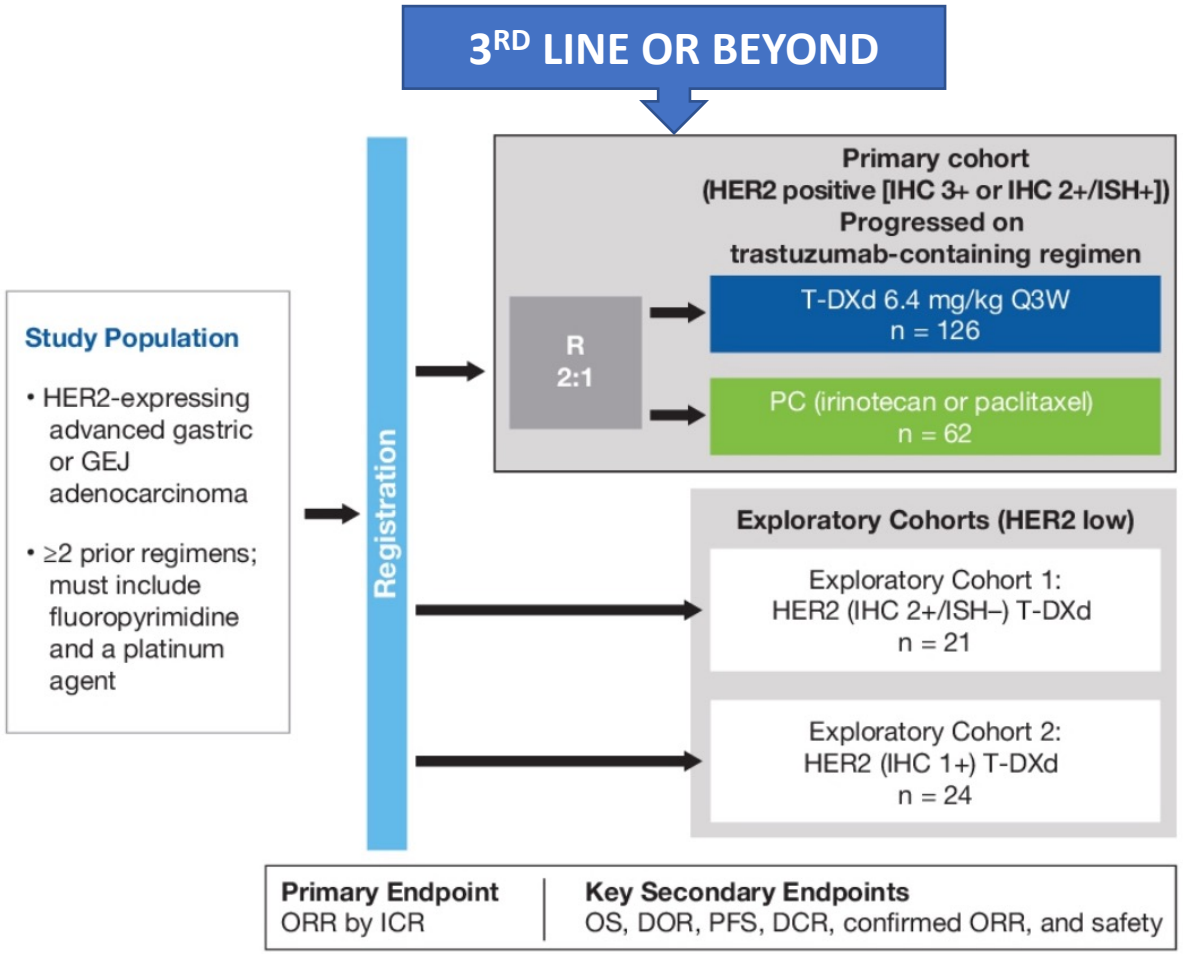
TO PRACTICE

Question 2

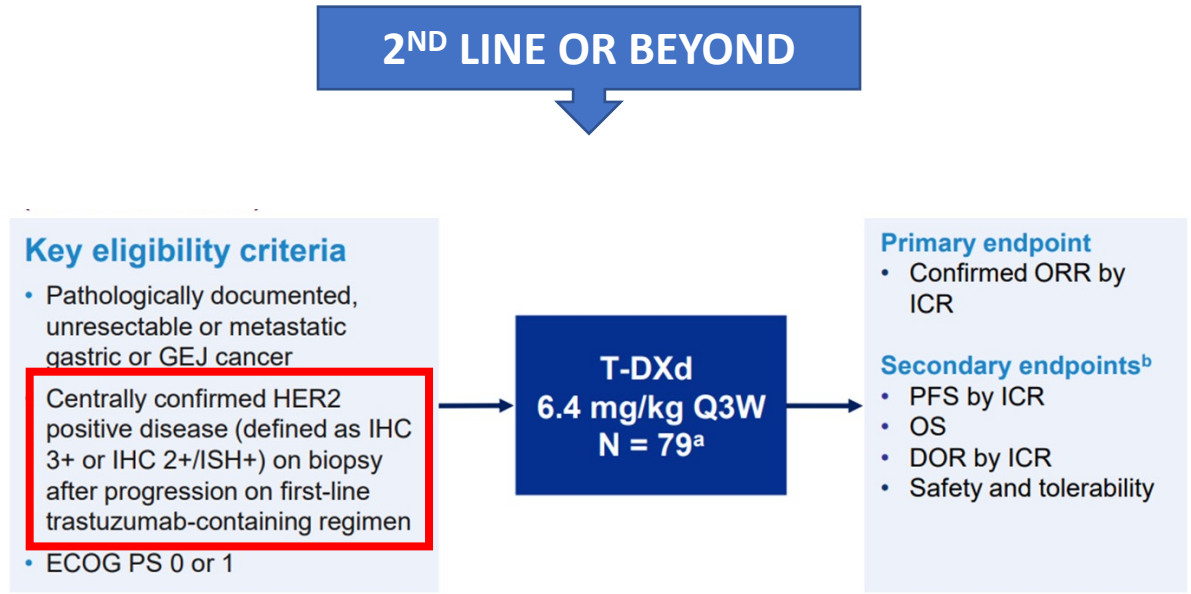
What is your usual first-line therapy for metastatic HER2-negative gastroesophageal cancer, and how do PD-L1 status, tumor location and histology factor into your decision?

	Esophageal	GEJ cancers	Gastric
Squamous cell carcinoma	• **Chemo+Nivo** • **Chemo+Pembro** • **Ipi+Nivo**	-	-
Adenocarcinoma	• **Chemo+Nivo (pref CPS≥5)** • **Chemo+Pembro (pref CPS≥10)** • **Chemo (CPS negative)**	• **Chemo+Nivo (pref CPS≥5)** • **Chemo+Pembro (pref CPS≥10)** • **Chemo (CPS negative)**	• **Chemo+Nivo (pref CPS≥5)** • **Chemo (CPS negative)**

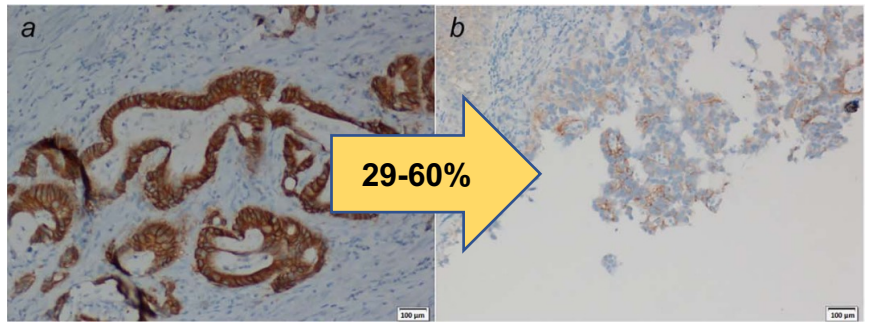
DESTINY STUDIES (T-DXd in GEAs)



DESTINY-Gastric01



DESTINY GASTRIC-02

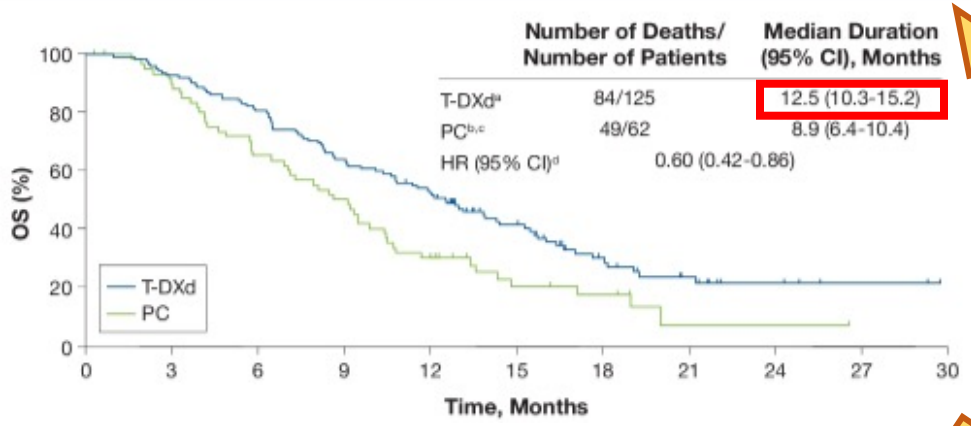


Bang YJ et al. GI ASCO 22; Ku G et al. ESMO 22

DESTINY STUDIES (T-DXd in GEAs)

OVERALL SURVIVAL

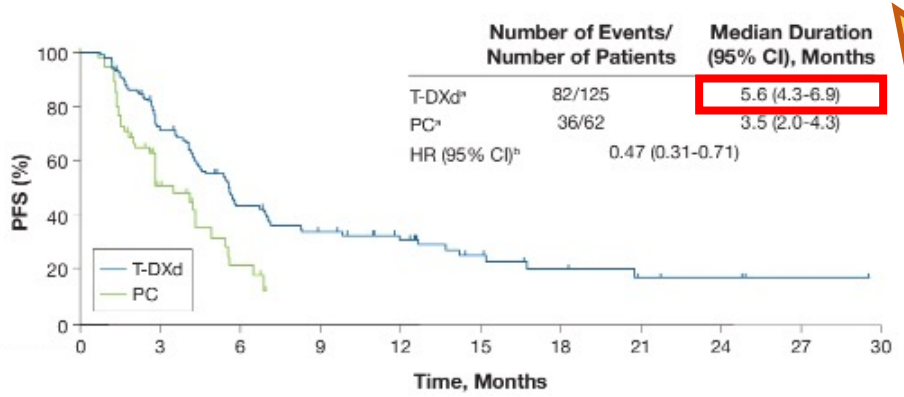
9.6 mos in RAINBOW



Response	T-DXd (n = 119)	PC (n = 56)
ORR* (CR + PR) by ICR, % (95% CI)	51.3† (41.9-60.5)	14.3 (6.4-26.2)
Confirmed ORR‡ (CR + PR) by ICR, % (95% CI) ▪ CR ▪ PR ▪ SD ▪ PD ▪ Not evaluable	42.9 (33.8-52.3) 8.4 34.5 42.9 11.8 2.5	12.5 (5.2-24.1) 0 12.5 50.0 30.4 7.1
Confirmed DCR (CR + PR + SD), % (95% CI)	85.7 (78.1-91.5)	62.5 (48.5-75.1)
Median confirmed DoR, mos (95% CI)	11.3 (5.6-NR)	3.9 (3.0-4.9)
Median time to response, mos (95% CI)	1.5 (1.4-1.7)	1.6 (1.3-1.7)

PROGRESSION FREE SURVIVAL

4.4 mos in RAINBOW



	Patients (N = 79)
Confirmed ORR[a], n (%)	**30 (38)** (95% CI, 27.3-49.6)
Confirmed best overall response, n (%)	
CR	**3 (3.8)**
PR	**27 (34.2)**
SD	**34 (43.0)**
PD	**13 (16.5)**
Not evaluable	**2 (2.5)**
Median DOR,[b] months	8.1 (95% CI, 4.1-NE)
Confirmed DCR[c], n (%)	64 (81.0) (95% CI, 70.6-89.0)
Median TTR, months	1.4 (95% CI, 1.4-2.6)
Median PFS,[d] months	5.5 (95% CI, 4.2-7.3)
Median follow up, months	5.7 (range, 0.7-15.2)

Bang YJ et al. GI ASCO 22; Ku G et al. ESMO 22

DESTINY-Gastric01 SAFETY

TEAEs in ≥20% of Patients Treated with T-DXd[a]

	T-DXd n = 125			PC Overall n = 62		
		Grade			Grade	
Preferred Term, %	Any	3	4	Any	3	4
Neutrophil count decreased[b]	64.8	38.4	12.8	35.5	16.1	8.1
Nausea	63.2	5.6	0	46.8	1.6	0
Decreased appetite	60.8	16.8	0	45.2	12.9	0
Anemia[c]	57.6	38.4	0	30.6	21.0	1.6
Platelet count decreased[d]	40.0	9.6	1.6	6.5	1.6	1.6
White blood cell count decreased[e]	38.4	20.8	0	35.5	8.1	3.2
Malaise	34.4	0.8	0	16.1	0	0
Diarrhea	32.8	2.4	0	32.3	1.6	0
Vomiting	26.4	0	0	8.1	0	0
Pyrexia	24.8	0	0	16.1	0	0
Constipation	24.8	0	0	24.2	0	0
Lymphocyte count decreased[f]	23.2	7.2	4.8	3.2	0	1.6
Alopecia	22.4	0	0	14.5	0	0
Fatigue	2[illegible]	7.2	0	24.2	3.2	0

69% with ram+paclitaxel

85.6%

56.5%

- **16 patients (12.8%) had T-DXd related ILD/pneumonitis: 13 Gr1 or 2; 2 Gr3 and 1 Gr4.**
- **1 T-DXd related death due to pneumonia**

Bang YJ et al. GI ASCO 22; Ku G et al. ESMO 22

Pembrolizumab with Chemotherapy Significantly Improved OS versus Chemotherapy Alone for HER2-Negative Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma Regardless of PD-L1 Expression

Press Release: February 16, 2023

"Today [results were announced] from the pivotal Phase 3 KEYNOTE-859 trial investigating pembrolizumab in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with HER2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma.

After a median follow-up of 31.0 months pembrolizumab in combination with chemotherapy significantly improved overall survival (OS), reducing the risk of death by 22% (HR = 0.78; $p < 0.0001$) compared to chemotherapy alone for these patients, regardless of PD-L1 expression. Median OS was 12.9 months for pembrolizumab plus chemotherapy versus 11.5 months for chemotherapy alone. These data are being presented today during a European Society for Medical Oncology (ESMO) Virtual Plenary and are being submitted to regulatory authorities worldwide."

https://www.merck.com/news/mercks-keytruda-pembrolizumab-plus-chemotherapy-significantly-improved-overall-survival-versus-chemotherapy-alone-in-patients-with-her2-negative-gastric-or-gastroesophageal-junction/

Discussion Question

How do you generally approach therapeutic sequencing for patients with metastatic HER2-positive gastroesophageal cancer?

RTP
RESEARCH
TO PRACTICE

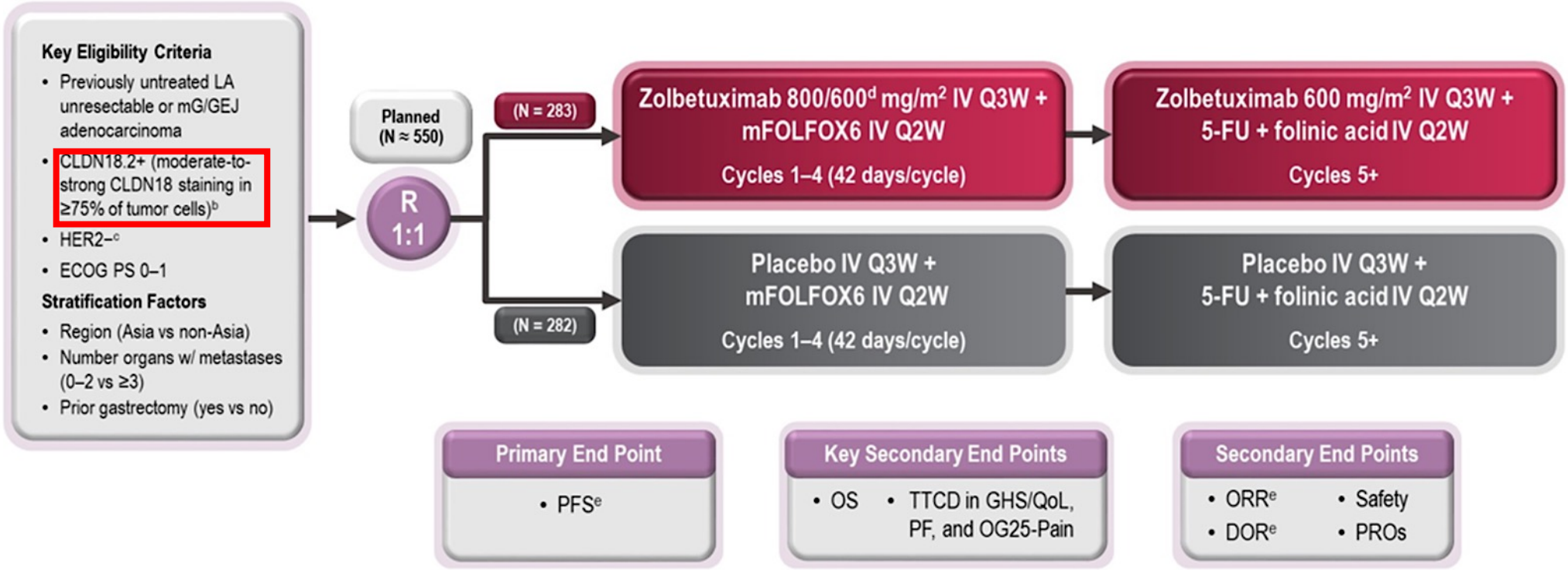
Question #3

How do you generally approach therapeutic sequencing for patients with metastatic HER2-positive gastroesophageal cancer?

- DESTINY-Gastric02 showed comparable efficacy with T-DXd as seen in Gastric01 study.
- Gastric02 study was 2nd line and patients were confirmed to be HER2 positive at enrollment.
- In HER2-positive patients, considering T-DXd may be reasonable as 2nd line treatment understanding that there are more safety concerns with the drug as compared to combination of ramucirumab and paclitaxel.
- If after progression on 1st line treatment, they no longer demonstrate HER2 positivity, ramucirumab/paclitaxel should still be standard practice.

“SPOTLIGHT” on Claudin 18.2

Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial



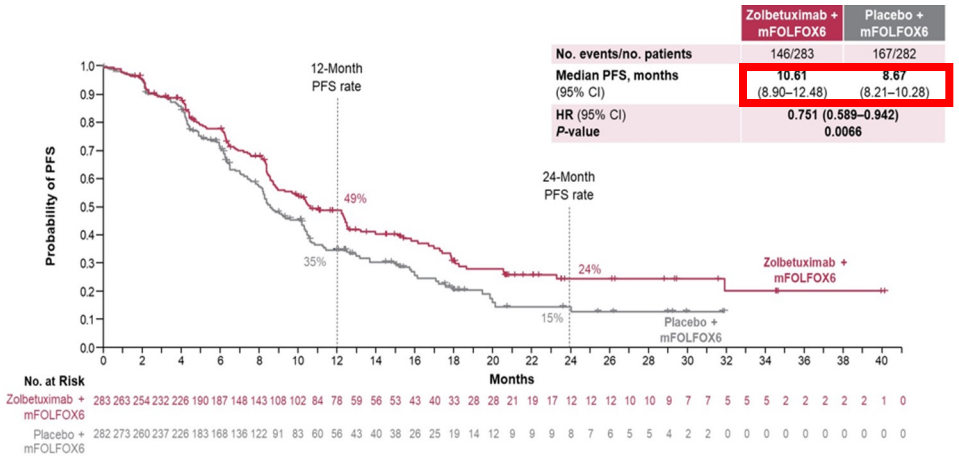
[a]Study was conducted at 215 sites in 20 countries across Australia, Asia, Europe, N. America, and S. America; [b]By central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing; [d]800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on cycle 1 day 22 and days 1 and 22 of subsequent cycles; [e]Per RECIST v1.1 by independent review committee.

77% had 0-2 metastases; 13.2% patients were tested to be PD-L1 CPS ≥5

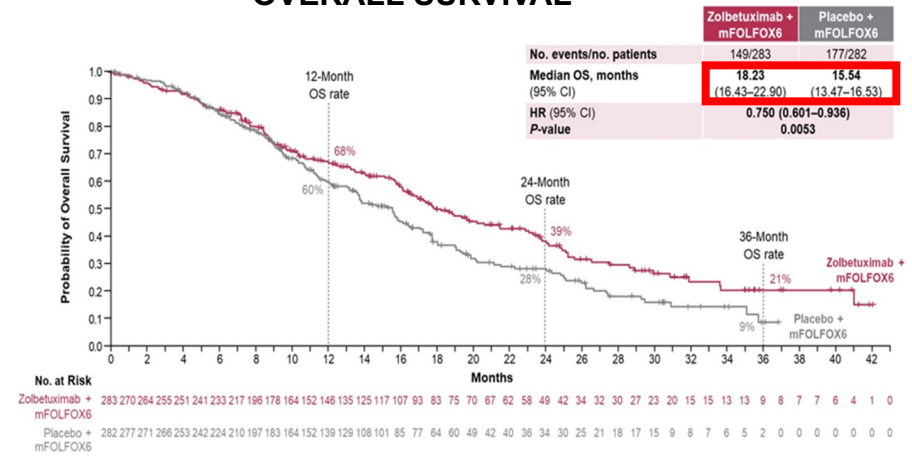
Shitara et al. GI ASCO 2023 LBA292

Zolbetuximab- Efficacy and Safety

PROGRESSION FREE SURVIVAL

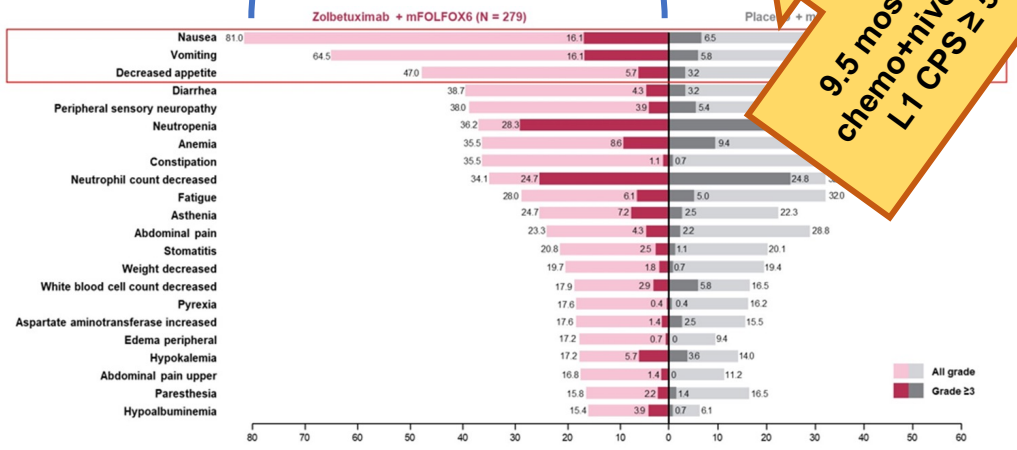


OVERALL SURVIVAL



	Zolbetuximab + mFOLFOX6 (N = 211)	Placebo + mFOLFOX6 (N = 211)
Patients[a], n	128	131
ORR[b], % (95% CI)	60.7 (53.72–67.30)	62.1 (55.17–68.66)
BOR[c,d], n (%)		
CR	12 (5.7)	7 (3.3)
PR	116 (55.0)	124 (58.8)
SD	45 (21.3)	52 (24.6)
PD	14 (6.6)	14 (6.6)
Median DOR[b], months, (95% CI)	8.51 (6.80–10.25)	8.11 (6.47–11.37)
3rd quartile, months (95% CI)	29.9 (10.41–NE)	15.5 (13.27–E)

86.7% ≥Gr AEs



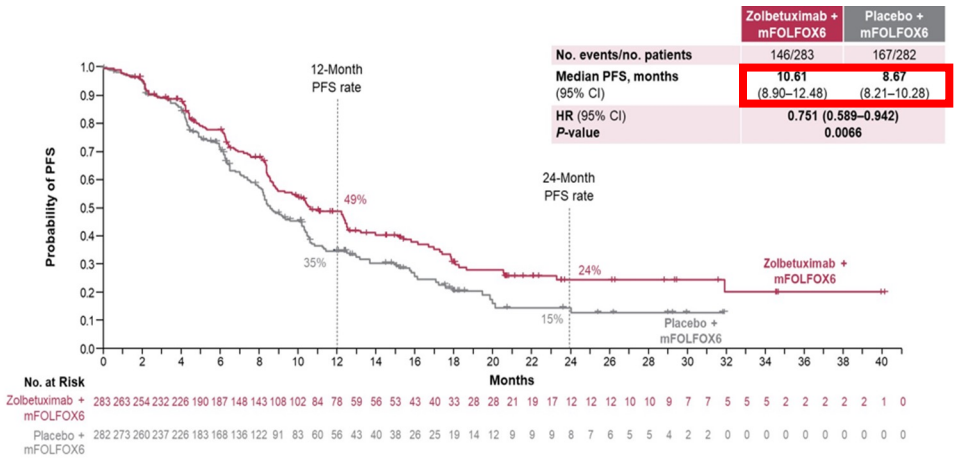
9.5 mos with chemo+nivo PD-L1 CPS ≥ 5

- The most common TEAEs with zolbetuximab + mFOLFOX6 were nausea and vomiting as on-target effects

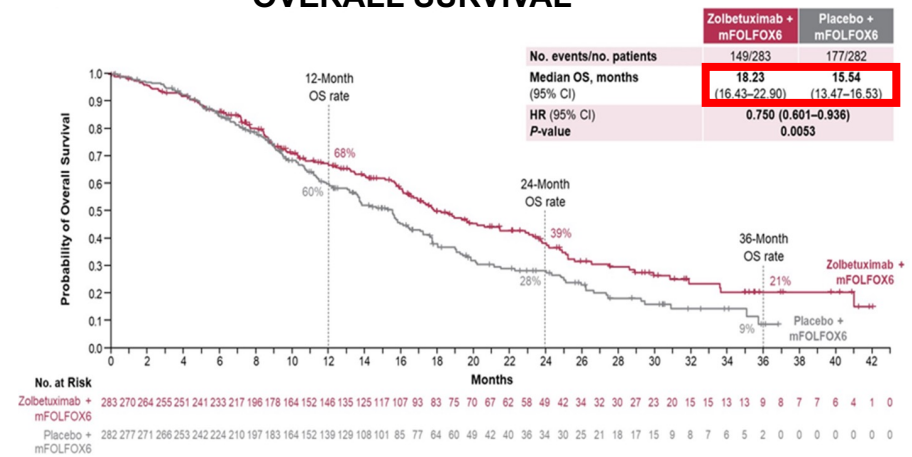
Shitara et al. GI ASCO 2023 LBA292

SPOTLIGHT vs CheckMate 649

PROGRESSION FREE SURVIVAL

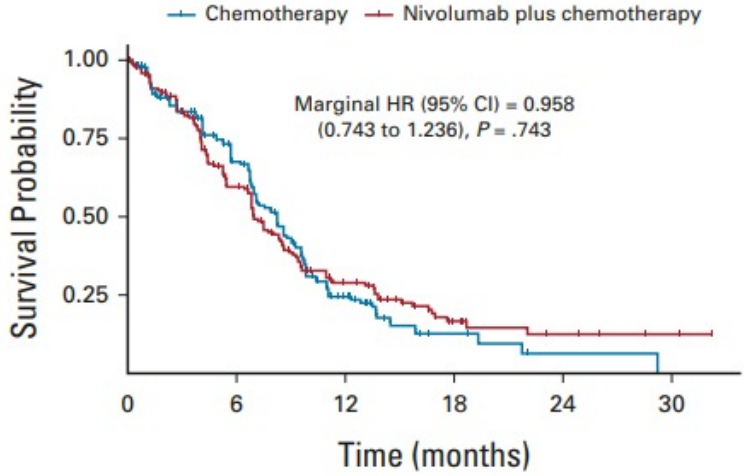


OVERALL SURVIVAL

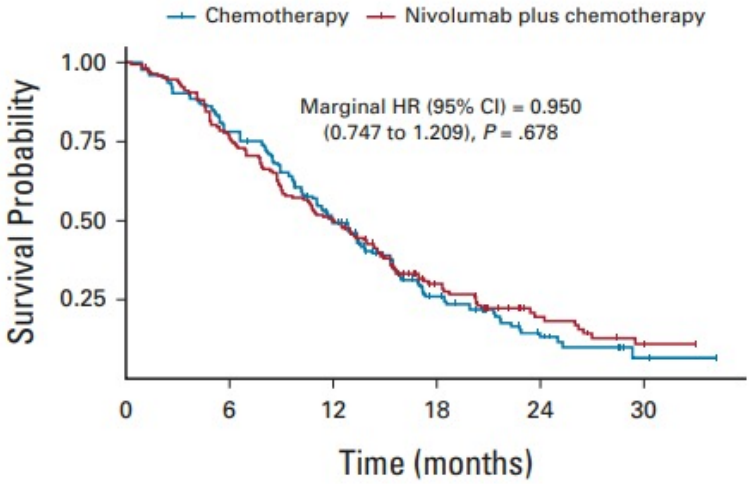


KM SUBTRACTION METHOD

PROGRESSION FREE SURVIVAL IN PD-L1 CPS 1-4



OVERALL SURVIVAL IN PD-L1 CPS 1-4



Shitara et al. GI ASCO 2023 LBA292, Zhao Y et al. JCO 2022

Discussion Question

If zolbetuximab were available, would you like to administer it to your patients with claudin 18.2-positive metastatic gastric/GEJ cancer? How will you most likely sequence it for your patients with high PD-L1 expression? What about for those with low PD-L1 expression?

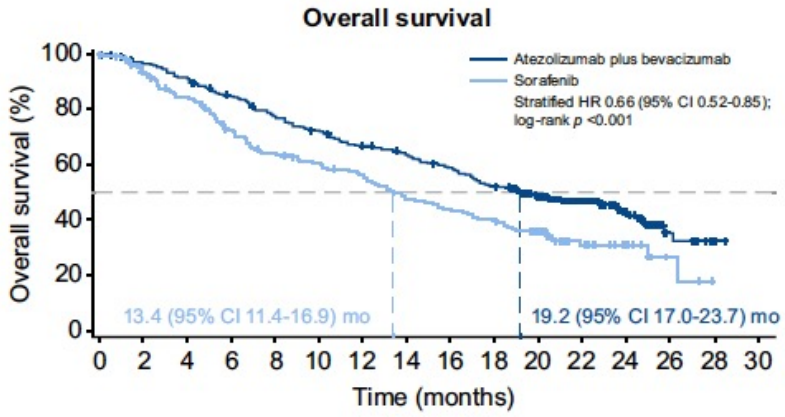
Question #4

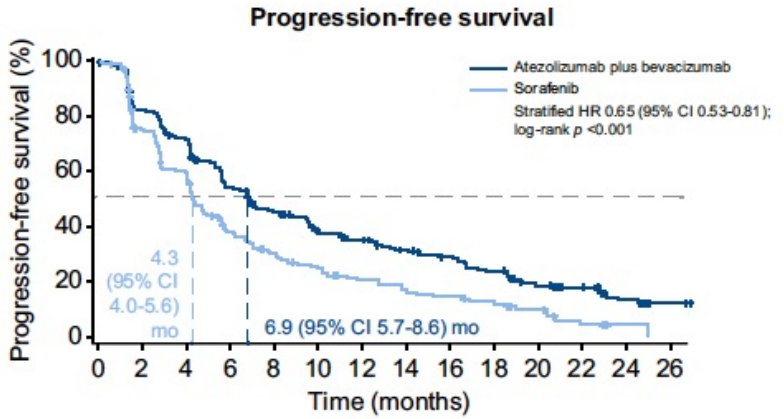
If zolbetuximab were available, would you like to administer it to your patients with claudin 18.2-positive metastatic gastric/GEJ cancer? How will you most likely sequence it for your patients with high PD-L1 expression? What about for those with low PD-L1 expression?

In Claudin 18.2 positive patients especially with low PD-L1, zolbetuximab when it becomes available is a good option. In high PD-L1 patients, factors such as side effects, burden of disease will play a role.

1L Treatment for Advanced HCC

IMbrave150

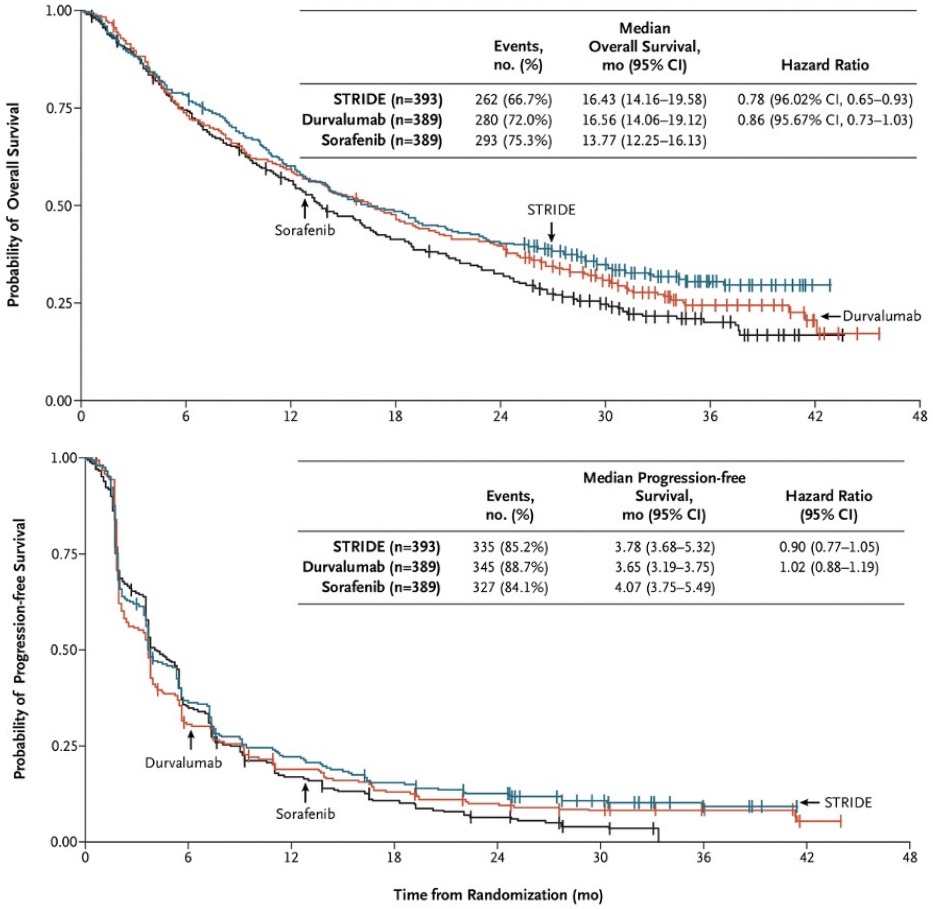




	Bev+Atezo	Durva+Tremi
mOS	**19.2 mos**	**16.43 mos**
mPFS	**6.9 mos**	**3.78 mos**
ORR	**30%**	**20%**

ORR 30% vs 11%

HIMALAYA



ORR 20% vs 17% vs 5%

Cheng A-L et al. J Hepatol 2022; Abou-Alfa GK et al. NEJM Evidence 2022

1L Treatment for IO intolerant or doublet IO therapy

	Sorafenib	Lenvatinib	Durvalumab	Pembrolizumab	Nivolumab
mOS	10.7 mos	13.6 mos	16.56 mos	17 mos	16.4 mos
mPFS	5.5 mos	8.9 mos	3.65 mos	4 mos	3.7 mos
ORR	2%	24.1%	17%	16%	15%
≥ Grade 3 AEs	45%	57%	37.1%	63%	23%

Contraindication to IO such as severe autoimmune condition or h/o transplant on immunosuppressive drugs

Cannot tolerate doublet immunotherapy and/or contraindication to anti-angiogenic therapy

Llovet JM NEJM 2008; Kudo M Lancet 2018; Abou-Alfa GK NEJM 2022; Verset G CCR 2022; Yau T Lancet Oncol 2022.

2L Treatment after progression on TKI

	Regorafenib	Cabozantinib	Ramucirumab (AFP ≥400 ng/ml)	Nivo 1 mg/kg + Ipi 3 mg/kg	Pembrolizumab	Nivolumab
mOS	**10.6 mos**	**10.2 mos**	**8.5 mos**	**22.8 mos**	**13.9 mos**	**15.0 mos**
mPFS	**3.1 mos**	**5.2 mos**	**2.8 mos**	**NR**	**3.0 mos**	**4.0 mos**
ORR	**7%**	**4%**	**5%**	**32%**	**18.3%**	**15%**
≥ Grade 3 AEs	**67%**	**68%**	**-**	**75%**	**52.7%**	**4%**

Response rates low. mOS less than 1 year. 2/3rds patients will have ≥ Gr3 AEs

For high AFP only

Increased rate of irAEs. Highest RR in 2L

15-20% patients respond. mOS ~1 yr.

Bruix J. Lancet 2017; Abou-Alfa NEJM 2018; Zhu A Lancet Oncol 2019; Yau T JAMA Oncol 2020; Finn R JCO 2019; El-Khoueiry AB Lancet 2017

Discussion Question

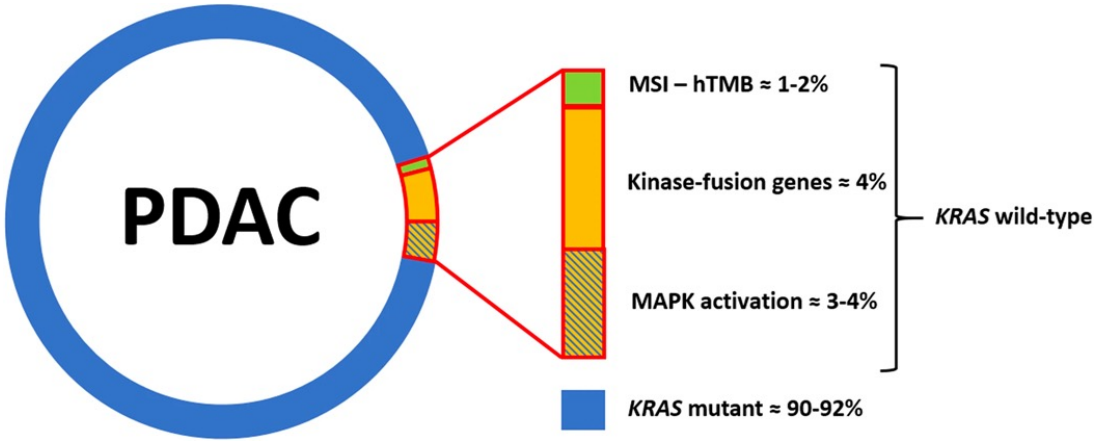
How do you choose between atezolizumab/bevacizumab and durvalumab/tremelimumab for your patients with newly diagnosed advanced hepatocellular carcinoma? In which situations do you administer a tyrosine kinase inhibitor as first-line therapy, and how do you sequence these agents for relapsed disease?

Question #5

How do you choose between atezolizumab/bevacizumab and durvalumab/tremelimumab for your patients with newly diagnosed advanced hepatocellular carcinoma? In which situations do you administer a tyrosine kinase inhibitor as first-line therapy, and how do you sequence these agents for relapsed disease?

- If patient cannot undergo EGD or has varices that cannot be treated, then would favor durva/tremi.
- TKI in 1L for patients not eligible for IO.
- No data currently for sequencing post bev/atezo or durva/tremi. But, would consider TKIs as subsequent therapy.

Spectrum of somatic mutations in PDAC

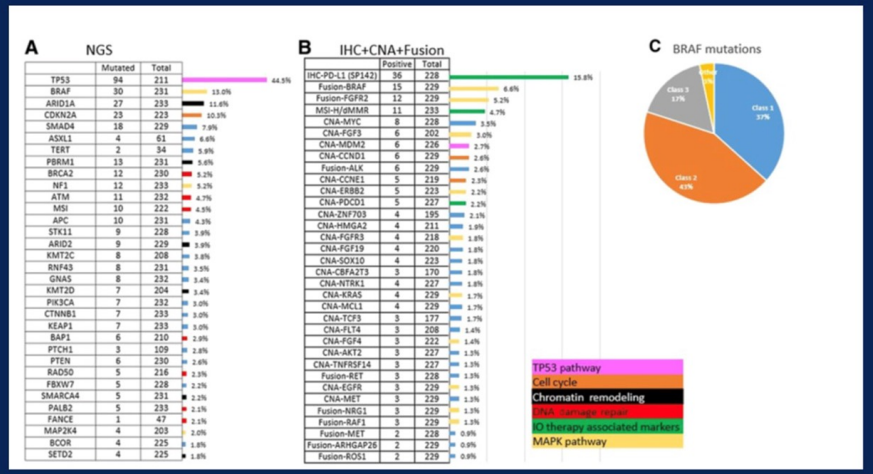


Luchini et al. 2020. J of Experimental and Clinical Cancer Research

Molecular characterization of KRAS wild type tumors

Most frequently mutated in KRAS-WT

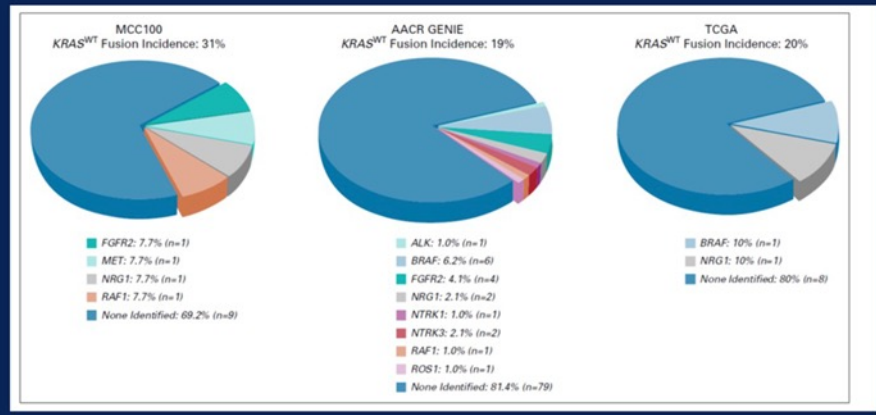
- TP53 44.5%
- BRAF 13%
  - 37% V600
  - 43% Ras independent/class 2
- More
  - MSI-H 4.7% vs. 0.7%
  - TMB-H 4.5% vs. 1%
  - Infiltration of CD8+T, NK, MD cells
- Mutations in
  - DDR genes (BRCA2m, ATM, BAP1, RAD50. FANCE, PALB2)
  - Chromatin remodeling (ARID1A, PBRM1, ARID2, KTM2D, KTM2C, SMARCA4, SETD2)
  - Cell cycle control (CDKN2A, CCND1, CCNE1)



Philip et al., CCR 2022

KRAS wild type tumors: Not only mutations, but:

- Amplifications:
  - FGF3 3%
  - FGFR3 1.8%
  - ERBB2 2.2%
  - MET 1.3%
  - NTRK 1.8%
- Gene fusions:
  - BRAF 6.6%
  - FGFR2 5.2%
  - ALK 2.6%
  - RET 1.3%
  - NRG 1.3%



Philip et al., CCR 2022; Fusco et al., JCO Precis Oncol 5, 2021

Algorithm for 1L treatment of PDAC

*- comprehensive panel e.g. PancNext, Pancreatic Cancer Panel or MyRisk
@- tissue next generation sequencing must be performed for all patients. If tissue is unavailable, circulating tumor DNA can be used.

All patients must undergo germline testing* as well as somatic testing@

Mutations in *BRCA* or *PALB2* or other homologous repair gene

- Prefer platinum-based treatment such as FOLFIRINOX, FOLFOX, gemcitabine/cisplatin
- Maintenance PARPi after 16 weeks of chemotherapy if there is no progressive disease

No mutations in HR genes

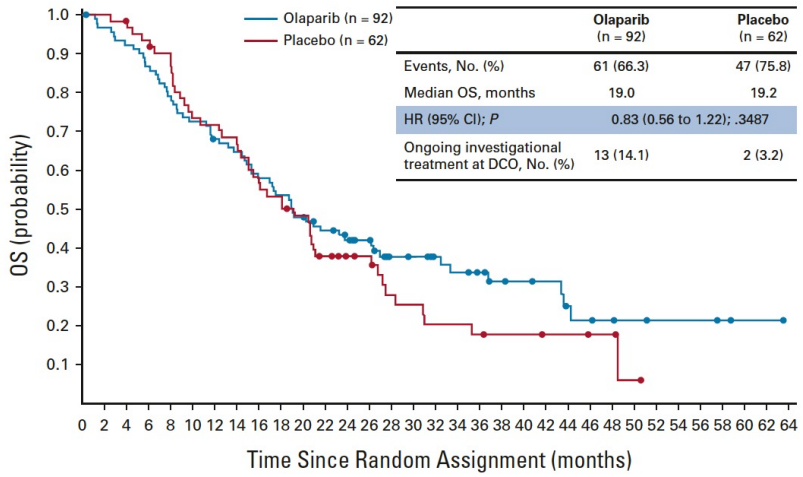
FOLFIRINOX or Gemcitabine +nab-paclitaxel

Germline mutations in PDAC

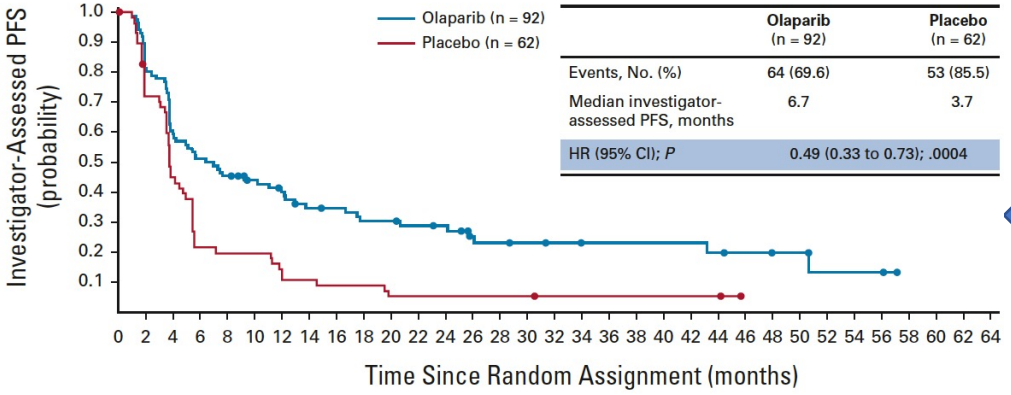
Gene name	Lifetime risk for pancreatic cancer
ATM	~5-10%
BRCA1	≤ 5%
BRCA2	5-10%
CDKN2A	> 15%
MSH2/MLH1/MSH6/PMS2	< 5-10%
PALB2	5-10%
STK11	> 15%
TP53	5-10%

1L maintenance therapy with PARPi in HR mutated PDAC

OLAPARIB MAINTENANCE IN g*BRCA1/2*



	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)



	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	

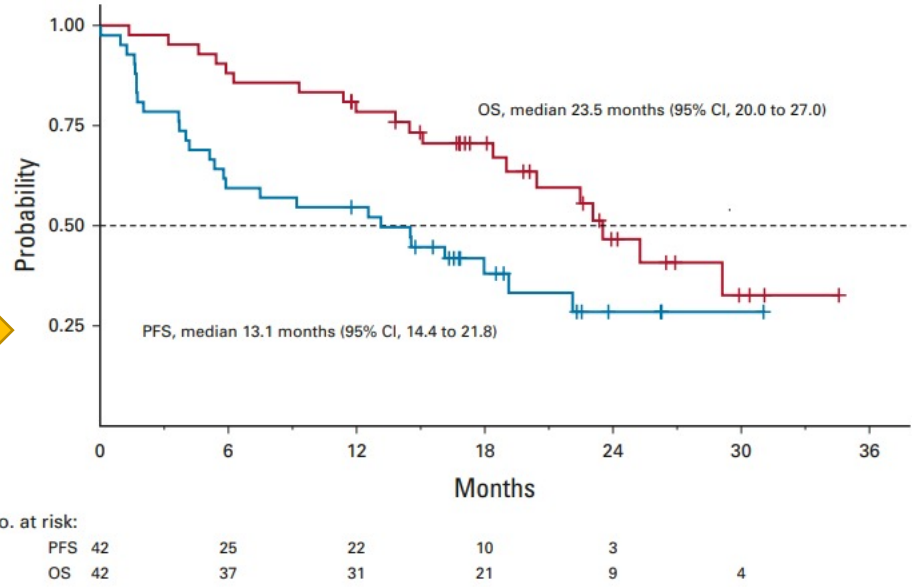
mOS 19.0 mos

mOS 23.5 mos

mPFS 13.1 mos

mPFS 6.7 mos

RUCAPARIB MAINTENANCE IN g*BRCA1/2*, g*PALB2* and s*BRCA2*



Kindler HL. JCO 2022; Reiss K JCO 2021

Discussion Question

Which patients with metastatic pancreatic adenocarcinoma (PAD) should undergo genetic testing, and what type (eg, germline versus somatic, panel versus one-off)? How should a PARP inhibitor such as olaparib be incorporated into treatment for appropriate patients with metastatic PAD and a germline BRCA mutation?

Question #6

Which patients with metastatic pancreatic adenocarcinoma (PAD) should undergo genetic testing, and what type (eg, germline versus somatic, panel versus one-off)? How should a PARP inhibitor (ie, olaparib) be incorporated into treatment for appropriate patients with metastatic PAD and a germline BRCA mutation?

- All newly diagnosed PDAC patients must undergo germline and somatic testing.
- Platinum-based chemotherapy must be offered for patients with *BRCA* or *PALB2* alterations
- Maintenance PARPi can be used in patients with *BRCA* or *PALB2* mutations that have not had progressive disease at 16 weeks after chemotherapy.