Updates in Treatment for Advanced Gastroesophageal Cancer

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Disclosures

- Speaking and Advisory Board: Exelixis, AstraZeneca
- Advisory Board: Seagen

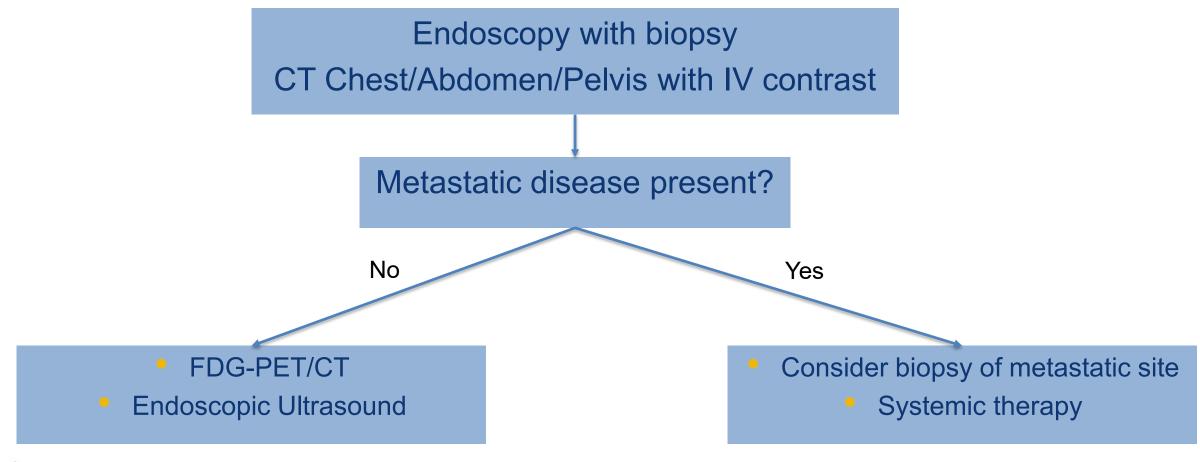


Outline

- Updates for Localized GE Cancers
- Immune Checkpoint Inhibitors in Advanced GE Cancers
- Targeted Therapies for Advanced GE Cancers
- Future Directions

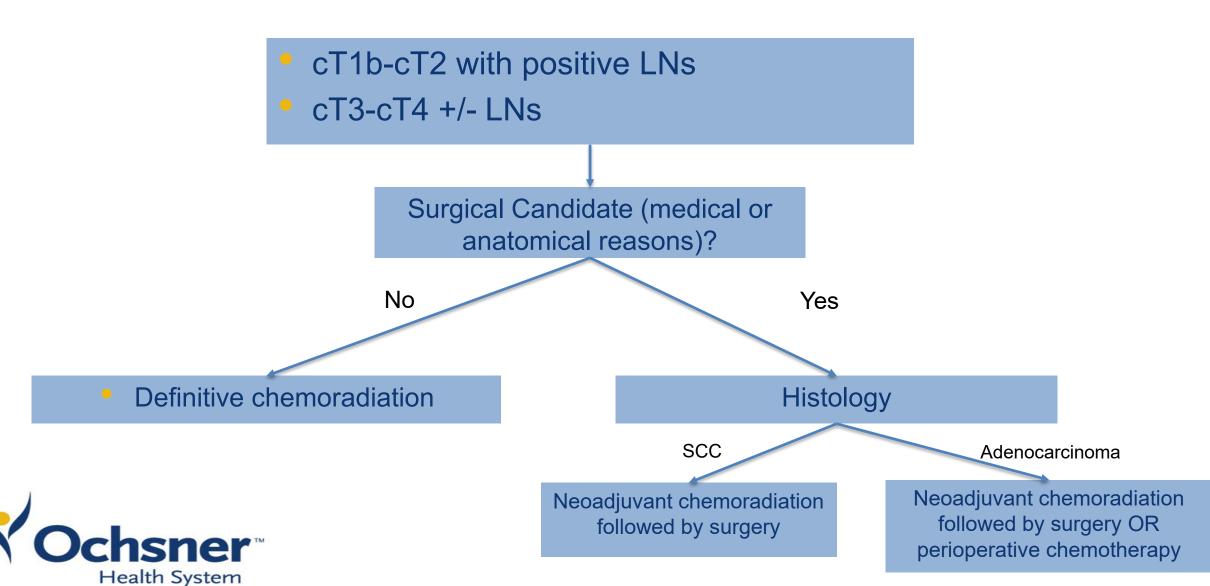


Diagnosis and Staging

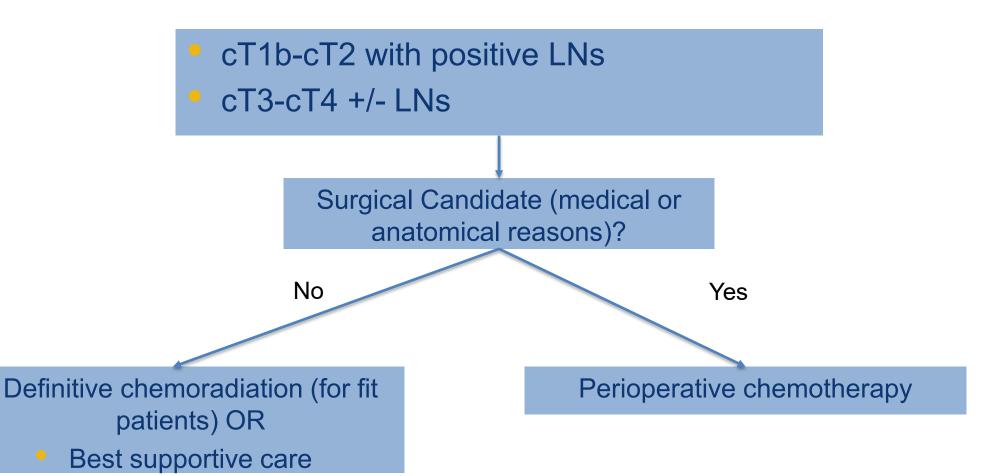




Treatment – Early Stage **Esophageal**



Treatment – Early Stage Gastric

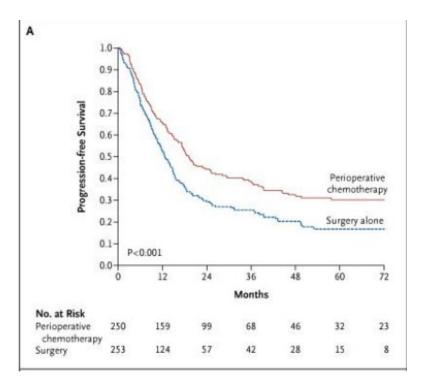




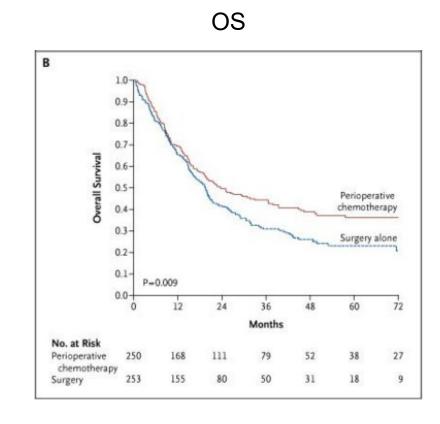
Early Stage - Gastric/GEJ/Distal Esophageal

MAGIC Trial – Perioperative ECF

PFS



Health System



Treatment – Early Stage Gastric/GEJ

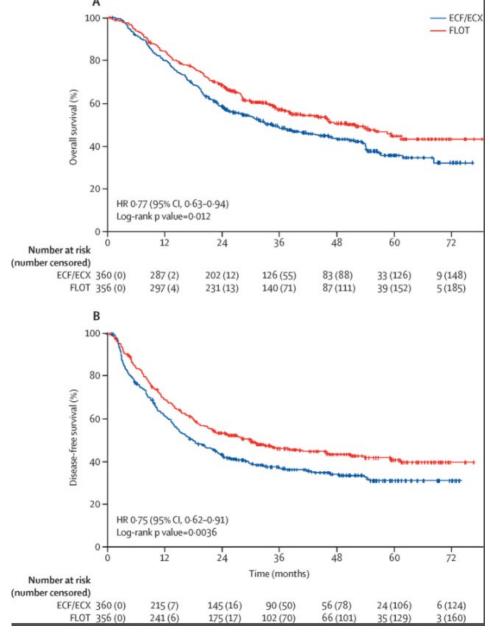
- FLOT4-AIO Trial
 - FLOT vs ECF
 - Docetaxel 50 mg/m2 + oxaliplatin 85 mg/m2 + leucovorin 200 mg/m2 + infusional 5-FU 2600 mg/m2 over 24 hours administered every 2 weeks
 - Studied FLOT x 4 cycle → Surgery → FLOT x 4 cycles
 - FLOT compared to ECF:
 - Higher pCR (16% vs 8%) in phase II portion
 - mOS 50m vs 35m (HR 0.77)
 - 3-year OS: 57% vs 48%



- FLOT4-AIO Trial
 - FLOT vs ECF

Health System

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Al-Batran et al. Lancet. 2019.

Treatment – Early Stage - Esophageal

CROSS Trial

- Randomized resectable esophageal and GEJ patients to surgery alone or chemoradiation
- Used carboplatin AUC 2 + paclitaxel 50 mg/m2 weekly x 5 weeks with 41.4 Gy XRT
- 75% adenocarcinoma
- R0 resection 92% vs 69% (P<0.001)
- pCR 29% of neoadjuvant CRT group

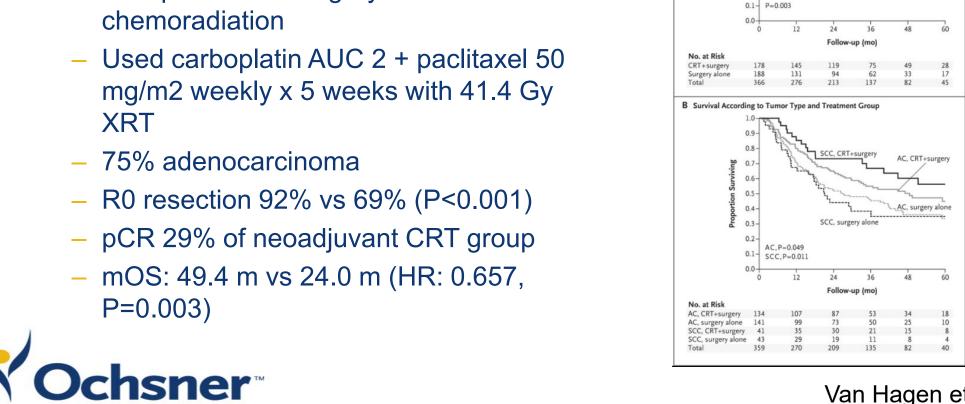


Treatment – Early Stage - Esophageal

CROSS Trial

Health System

 Randomized resectable esophageal and GEJ patients to surgery alone or chemoradiation



A Survival According to Treatment Group

Standard of care for early stage (≥ T2 or N+, M0) gastric or GEJ (Siewart 3 +/- 2) adenocarcinoma is:

FLOT x 4
$$\rightarrow$$
 SURGERY \rightarrow FLOT x 4

- ** Only for most fit patients
- ** For less fit patients, consider perioperative FOLFOX or CAPOX based on CLASSIC trial
 - Data extrapolated from adjuvant CLASSIC trial

Standard of care for early stage esophageal (≥ T2 or N+, M0) or GEJ (Siewart 1 +/-2) SCC or adenocarcinoma is:

Chemoradiation (carboplatin + paclitaxel) → SURGERY → NIVOLUMAB

** For patients who do not achieve pCR



CheckMate 577 study design

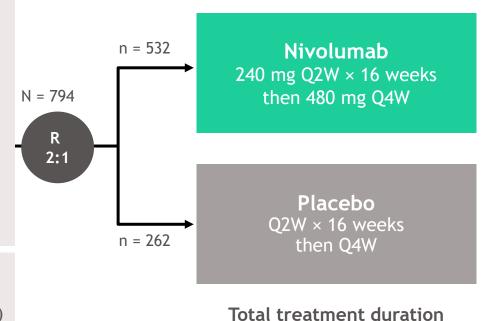
• CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled triala

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
 - \geq ypT1 or \geq ypN1
- ECOG PS 0-1

Stratification factors

- Histology (squamous versus adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 versus ypN0)
- Tumor-cell PD-L1 expression (≥ 1% versus < 1%c)



of up to 1 yeard

Primary endpoint:

DFS^e

Secondary endpoints:

- OSf
- OS rate at 1, 2, and 3 years

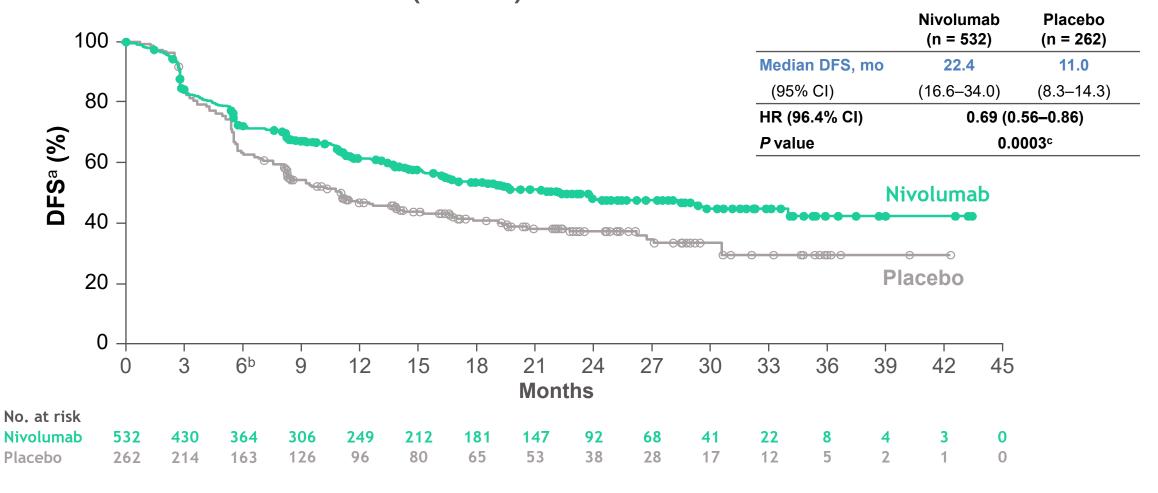
Exploratory endpoints included:

- Safety
- DMFSg
- PFS2^h
- QoL

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



Disease-free survival (DFS)





Disease-free survival subgroup analysis

Category		Median DFS, mo				
	Subgroup	Nivolumab	Placebo	Unstratified HR	Unstratified HR (95% CI)	
Overall	N = 794	22.4	11.0	0.70		
Fumor location at initial diagnosis	Esophagus (n = 462)	24.0	8.3	0.61	-	
	Gastroesophageal junction (n = 332)	22.4	20.6	0.87		
Histologic type	Adenocarcinoma (n = 563)	19.4	11.1	0.75		
	Squamous cell carcinoma (n = 230)	29.7	11.0	0.61		
Tumor cell PD-L1 expression ^a	≥ 1% (n = 129)	19.7	14.1	0.75		
	< 1% (n = 570)	21.3	11.1	0.73	 -	
	Indeterminate/nonevaluable (n = 95)	Not reached	9.5	0.54		
PD-L1 CPS expression ^{a,b}	≥ 5 (n = 371)	29.4	10.2	0.62	→	
	< 5 (n = 295)	16.3	11.1	0.89	>- -	
	Missing/nonevaluable (n = 128)	Not reached	10.8	0.61		
Pathologic lymph node status	ypN0 (n = 336)	Not reached	27.0	0.74		
	≥ ypN1 (n = 457)	14.8	7.6	0.67	- ◆-	
Pathological tumor status	ypT0 (n = 47)	34.0	5.2	0.35	-	
	ypT1 or ypT2 (n = 308)	28.3	9.3	0.60	—	
	ypT3 or ypT4 (n = 436)	18.9	14.1	0.84	- ◆ - †	
Time from complete	< 10 weeks (n = 256)	24.0	14.1	0.84		
esection to randomization	≥ 10 weeks (n = 538)	21.4	10.8	0.66	→ !	
Radiotherapy dosage ^{b,c}	< 41.4 Gray (n = 92 ^d)	19.7	13.8	0.69		
	41.4-50.4 Gray (n = 504)	24.0	11.1	0.73	<u> </u>	
	> 50.4 Gray (n = 152)	21.4	8.3	0.72		
	Not reported (n = 41)	14.4	6.1	0.41	<u></u>	



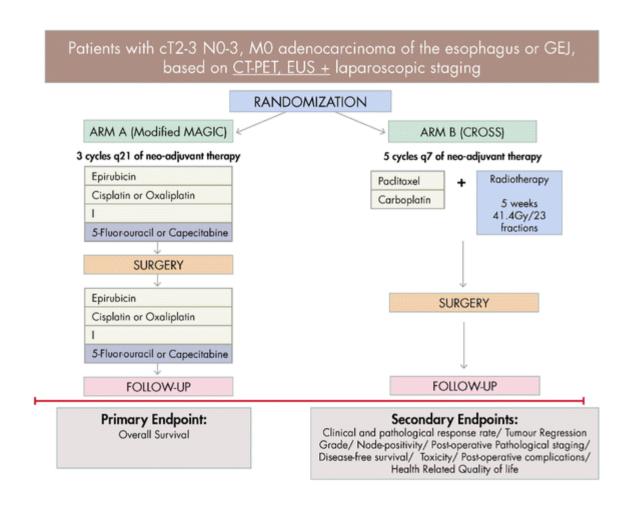
Unanswered question:

Is perioperative chemotherapy (i.e. FLOT) superior to neoadjuvant chemoradiation (i.e. CROSS regimen)?



Neo-AEGIS trial:

- Patients with adenocarcinoma of esophagus or GEJ
- Most patients in chemotherapy arm received MAGIC regimen (ECF) vs FLOT (157 vs 27).





Neo-AEGIS trial:

- Estimated 3 year survival of ChemoRT vs chemo:
 - 56% vs 57%, HR 1.02 (95% CI: 0.74-1.42)
- Authors concluded there was non-inferiority between two approaches

	Arm A (Magic/FLOT)	Arm B CROSS
R0 (negative margins)	82%	95%
ypN0	44.5%	60.1%
Tumor regression grade 1 & 2	12.1%	41.7%
Pathologic complete response	5%	16%
Neutropenia (Gr 3/4)	14.1%	2.8%
Neutropenic sepsis	2.7%	0.6%
Postoperative in-hospital deaths	3%	3%
Postoperative Pneumonia/ARDS	20%/0.6%	16%/4.3%
Anastomotic Leak	12%	11.7%
Clavien-Dindo > III <v< td=""><td>23.6%</td><td>22%</td></v<>	23.6%	22%
2021 by American Society of Clir	nical Oncology	



Still unanswered question:

Is perioperative chemotherapy (i.e. FLOT) superior to neoadjuvant chemoradiation (i.e. CROSS regimen)?

Well...

If FLOT > MAGIC (FLOT4-AIO)

And MAGIC = CROSS (Neo-Aegis)

Then FLOT > CROSS ??



Treatmen

Perhaps. ES esophageal a

But ESOPEC So....

Health System



Treatment - M

- Two year sidine + platinum (i.e. FOLT and of care first-live)
- Per liab was a line therapy for adenocarch PD-L1 ≥ 1
- Niv was approved as 2^{no} sophageal SCC index of PD-L1.

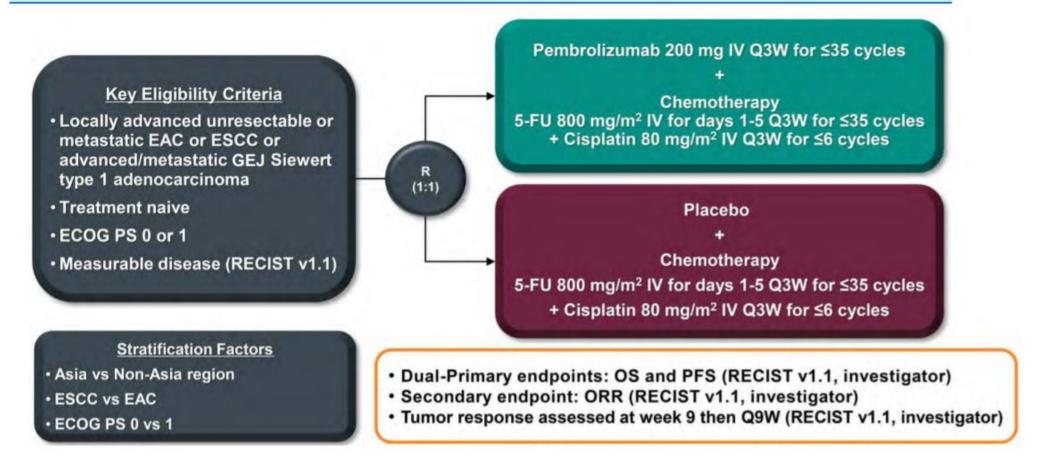


Treatment - Metastatic

- Immunotherapy Trials:
 - KEYNOTE 590 Esophageal Cancer (adeno & squamous)
 - CHECKMATE 648 Esophageal SCC
 - CHECKMATE 649 Gastric and Esophageal Adenocarcinoma

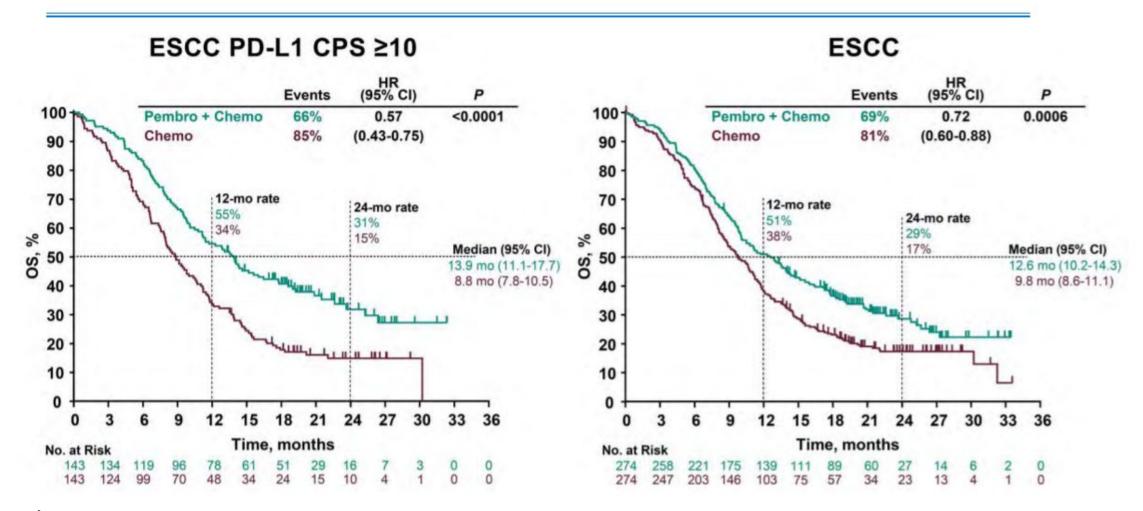


First-Line Metastatic Esophageal Cancer – KEYNOTE-590



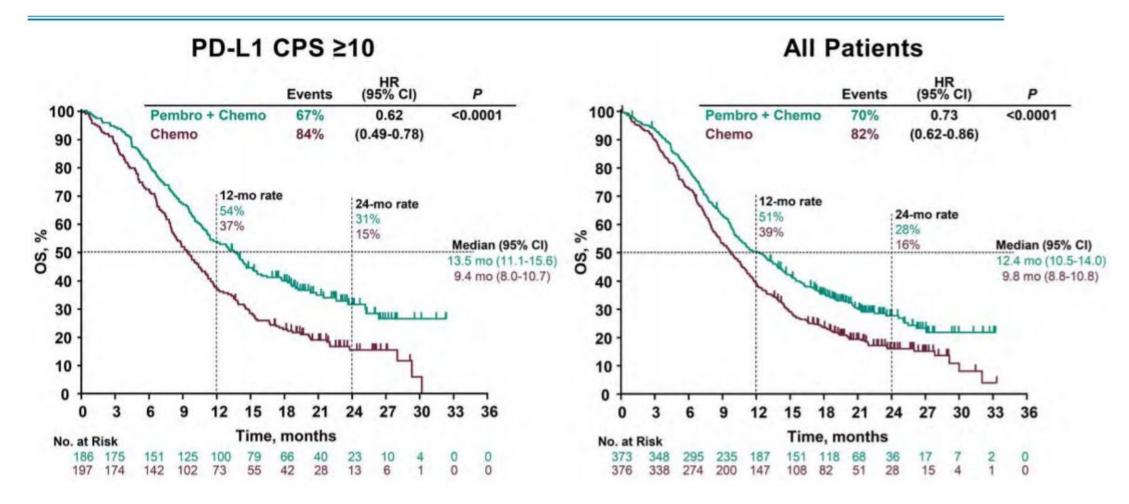


KEYNOTE-590 – Overall Survival in SCC Patients





KEYNOTE-590 – Overall Survival in All Patients





KEYNOTE-590 – Subgroup Analyses

	Ove	rall S	urvival		Progress	sion-fr	ee Surviva
	Events/Pation	ents, N	HR (95% CI)		Events/Patie	nts, N	HR (95% CI)
Overall	571/749	+=+	0.73 (0.62-0.86)	Overall	630/749	184	0.65 (0.55-0.76)
Age, years		100		Age, years			
< 65	332/427	-	0.76 (0.61-0.95)	< 65	372/427	-	0.69 (0.56-0.85)
≥ 65	239/322	-	0.69 (0.53-0.89)	≥65	258/322		0.62 (0.48-0.80)
Sex				Sex			
Male	482/625	H=+	0.70 (0.58-0.84)	Male	537/625	H#+1	0.63 (0.53-0.75)
Female	89/124	-	0.89 (0.59-1.35)	Female	93/124	-	0.74 (0.49-1.12)
ECOG PS				ECOG PS		7.5	
0	207/299	-	0.72 (0.55-0.94)	0	248/299	H=H	0.57 (0.45-0.74)
1	362/448	-	0.73 (0.59-0.90)	1	380/448	H#H	0.71 (0.58-0.87)
Geographic region				Geographic region			
Asia	288/393	-	0.64 (0.51-0.81)	Asia	333/393	H=H	0.59 (0.47-0.73)
Non-Asia	283/356	-	0.83 (0.66-1.05)	Non-Asia	297/356		0.70 (0.56-0.89)
Histology			And an area	Histology			
Adenocarcinoma	159/201	-	0.74 (0.54-1.02)	Adenocarcinoma	167/201		0.63 (0.46-0.87)
ESCC	412/548	-	0.72 (0.60-0.88)	ESCC	463/548	H#H	0.65 (0.54-0.78)
PD-L1 Status		200		PD-L1 Status			
CPS ≥10	289/383	H=H	0.62 (0.49-0.78)	CPS ≥10	314/383	H=H	0.51 (0.41-0.65)
CPS <10	271/347	-	0.86 (0.68-1.10)	CPS <10	302/347	H=	0.80 (0.64-1.01)
	0.1	1	10		0.1	1	10
	Favors pen		Favors chemo		Favors pe		Favors chemo



CheckMate 648 study design

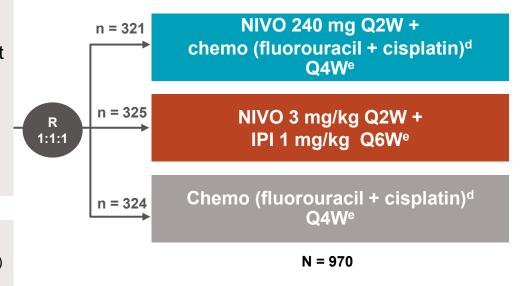
CheckMate 648 is a global, randomized, open-label phase 3 study^a

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:

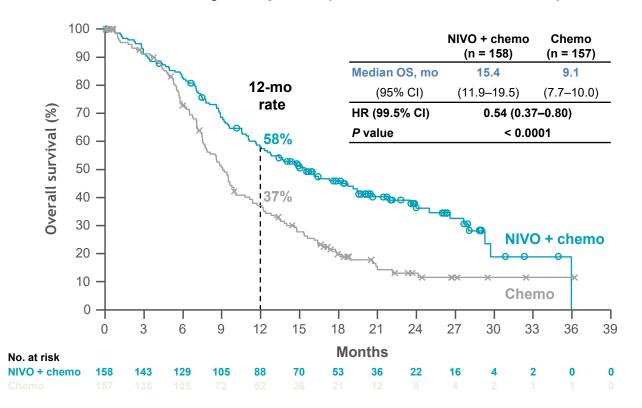
- OS and PFS^f (all randomized)
- ORR^f (tumor cell PD-L1 ≥ 1% and all randomized)

At data cutoff (January 18, 2021), the minimum follow-up was 12.9 monthsg

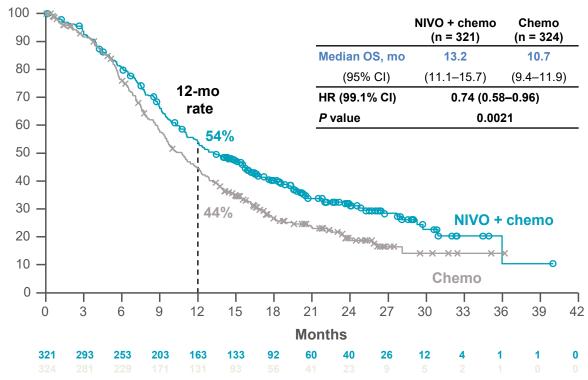


Overall survival: NIVO + chemo vs chemo

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



All randomized^a





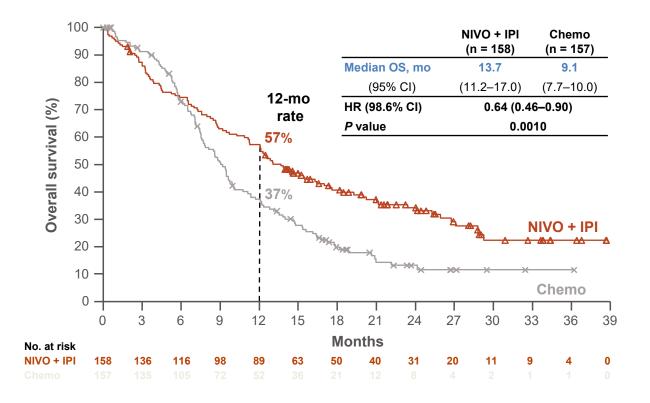
Overall survival subgroup analysis: NIVO + chemo vs chemo

Category (all randomized)	Subaroup	Median OS, months		Unstratified HR for	Unatratifical LID (05% CIV	
	Subgroup	NIVO + chemo	Chemo	death	Unstratified HR (95% C	
Overall (N = 645)	·	13.2	10.7	0.74	-	
Age, years	< 65 (n = 333)	11.8	10.2	0.80		
	\geq 65 (n = 312)	15.1	11.0	0.67		
Sex	Male (n = 528)	12.5	10.0	0.70		
	Female (n = 117)	15.2	14.8	1.02		
Geographic region	Asian (n = 451)	15.5	11.9	0.74		
	Non-Asian (n = 194)	10.5	8.5	0.74		
ECOG PS ^a	0 (n = 300)	17.3	12.4	0.71		
	1 (n = 344)	10.6	9.0	0.76		
Tumor cell PD-L1 expression ^b	≥ 1% (n = 314)	15.4	9.2	0.55		
	< 1% (n = 329)	12.0	12.2	0.98	<u> </u>	
	≥ 5% (n = 235)	13.7	9.5	0.61		
	< 5% (n = 408)	12.8	11.1	0.82		
	≥ 10% (n = 199)	14.7	9.5	0.62		
	< 10% (n = 444)	12.3	10.8	0.79		
Disease status at study entry	De novo metastatic (n = 371)	13.4	9.4	0.63		
	Recurrent – locoregional (n = 46)	14.8	13.5	0.91		
	Recurrent – distant (n = 132)	12.3	12.8	1.00		
	Unresectable advanced (n = 96)	12.8	12.1	0.73	•	
No. of organs with metastases	≤ 1 (n = 316)	15.7	11.6	0.74	 -	
	≥ 2 (n = 329)	11.1	9.6	0.72		
Smoking	Current or former (n = 510)	12.3	10.0	0.76		
	Never or unknown (n = 135)	15.7	11.1	0.63		

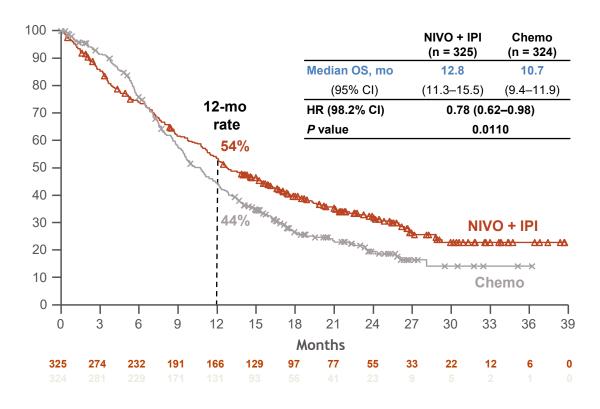


Overall survival: NIVO + IPI vs chemo

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



All randomized^a





Overall survival subgroup analysis: NIVO + IPI vs chemo

Catagory (all randomized)	Subaroun	Median OS, months		Unstratified HR for	Unaturatified UD (05% CI)	
Category (all randomized)	Subgroup	NIVO + IPI	Chemo	death	Unstratified HR (95% CI)	
Overall (N = 649)	•	12.8	10.7	0.78		
Age, years	< 65 (n = 351)	12.1	10.2	0.92		
	≥ 65 (n = 298)	16.0	11.0	0.63		
Sex	Male (n = 544)	13.7	10.0	0.70	—	
	Female (n = 105)	11.7	14.8	1.36	+	
Geographic region	Asian (n = 455)	13.7	11.9	0.83		
	Non-Asian (n = 194)	11.4	8.5	0.69		
ECOG PS ^a	0 (n = 300)	17.0	12.4	0.73		
	1 (n = 348)	9.7	9.0	0.81		
Tumor cell PD-L1 expression ^b	≥ 1% (n = 314)	13.7	9.2	0.63		
	< 1% (n = 330)	12.0	12.2	0.96		
	≥ 5% (n = 235)	13.0	9.5	0.66		
	< 5% (n = 409)	12.4	11.1	0.86	- • 	
	≥ 10% (n = 200)	13.0	9.5	0.71		
	< 10% (n = 444)	12.5	10.8	0.82	—	
Disease status at study entry	De novo metastatic (n = 383)	12.1	9.4	0.75		
•	Recurrent – locoregional (n = 50)	13.9	13.5	1.13	-	
	Recurrent – distant (n = 133)	15.5	12.8	0.88	• !	
	Unresectable advanced (n = 83)	17.4	12.1	0.63	- !	
No. of organs with metastases	≤ 1 (n = 318)	16.0	11.6	0.76	•	
-	≥ 2 (n = 331)	10.3	9.6	0.81	-	
Smoking	Current or former (n = 524)	14.4	10.0	0.74	-	
•	Never or unknown (n = 125)	9.8	11.1	1.01		

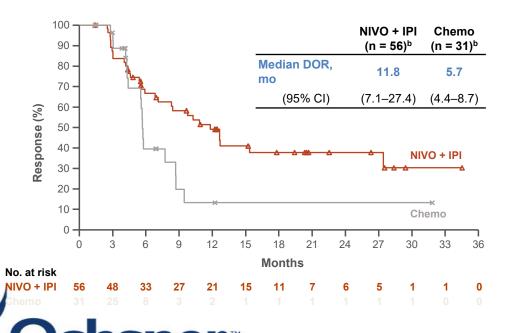


Chau et al. ASCO Annual Meeting 2021.

Response and duration of response: NIVO + IPI vs chemo

Tumor cell PD-L1 ≥ 1%

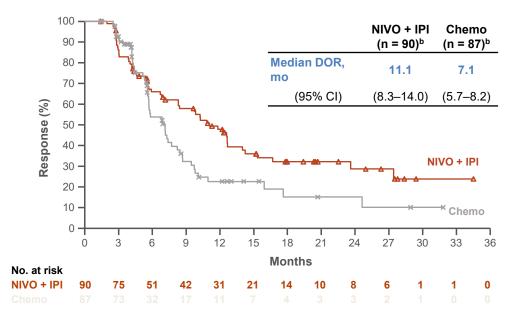
Response per BICR	NIVO + IPI (n = 158)	Chemo (n = 157)		
ORR, % (95% CI)	35 (28-43)	20 (14–27)		
CRa	18	5		
PR ^a	18	15		
SD	27	46		
PD	30	15		



Health System

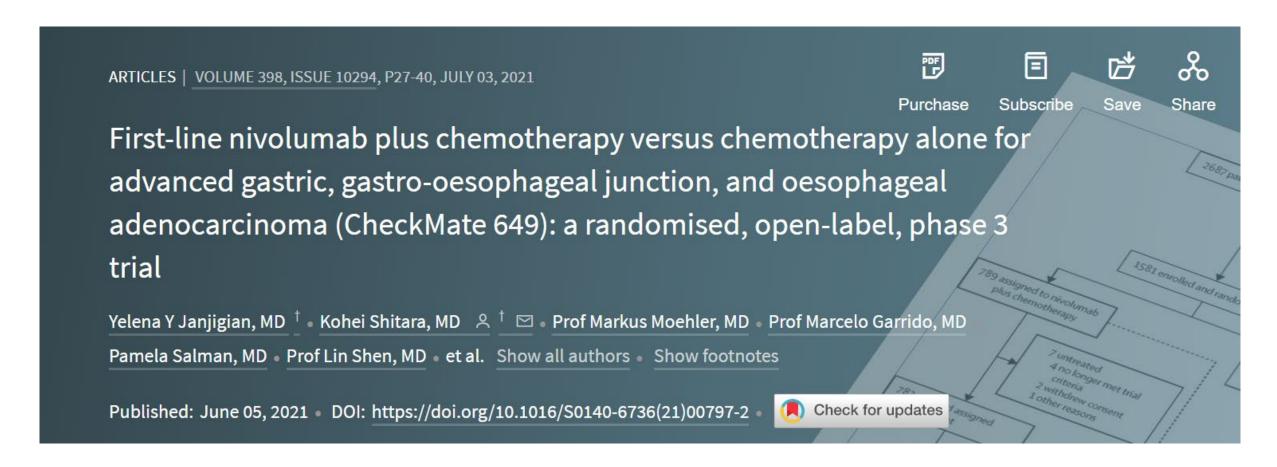
All randomized

Response per BICR	NIVO + IPI (n = 325)	Chemo (n = 324)		
ORR, % (95% CI)	28 (23–33)	27 (22–32)		
CR	11	6		
PR	17	21		
SD	32	46		
PD	32	12		



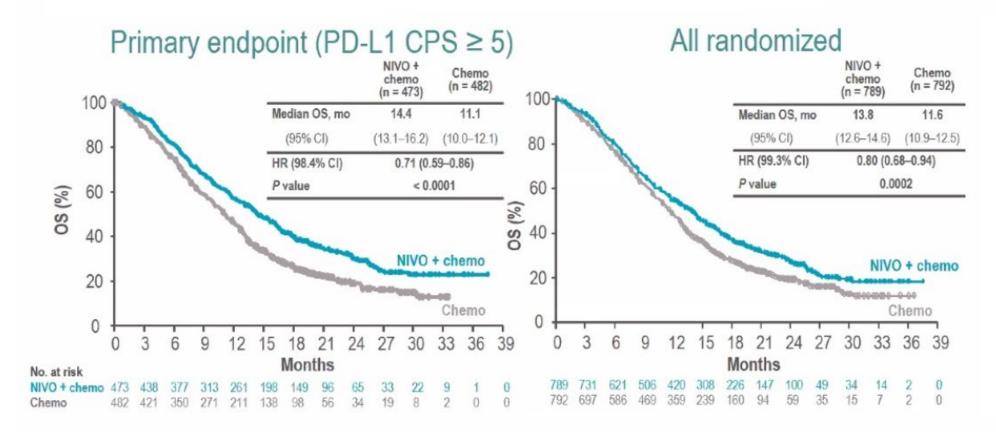
Chau et al. ASCO Annual Meeting 2021.

Treatment – Metastatic





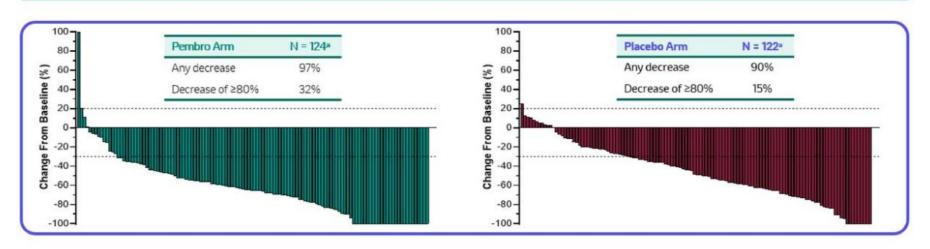
Overall survival in Checkmate-649





Treatment - Metastatic

KEYNOTE-811: KEYTRUDA+trastuzumab+chemotherapy becomes new treatment option for HER2+ metastatic gastric/GEJ cancer

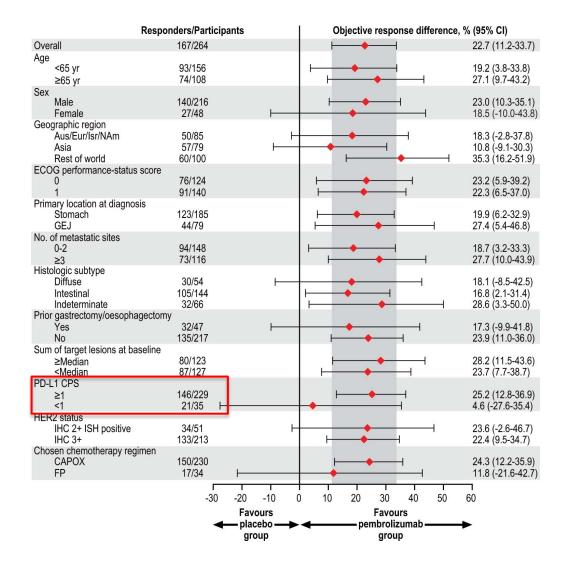


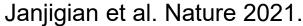
- Results support FDA accelerated approval in May 2021
- Pembrolizumab plus trastuzumab and chemotherapy provided a 74.4% ORR that resulted in a statistically significant, clinically meaningful 22.7% improvement in ORR compared with placebo plus trastuzumab and chemotherapy
- · Responses to pembrolizumab plus trastuzumab and chemotherapy were deeper and more durable
- Study is continuing as planned, and analyses of OS and PFS will be performed in the future in accordance with the analysis plan



Treatment – Metastatic

- Complete Response:
 - 11.3% in pembro arm vs 3.1% in placebo arm
- Duration of Response:
 - 10.6 months in pembro arm vs 9.5 months in placebo arm

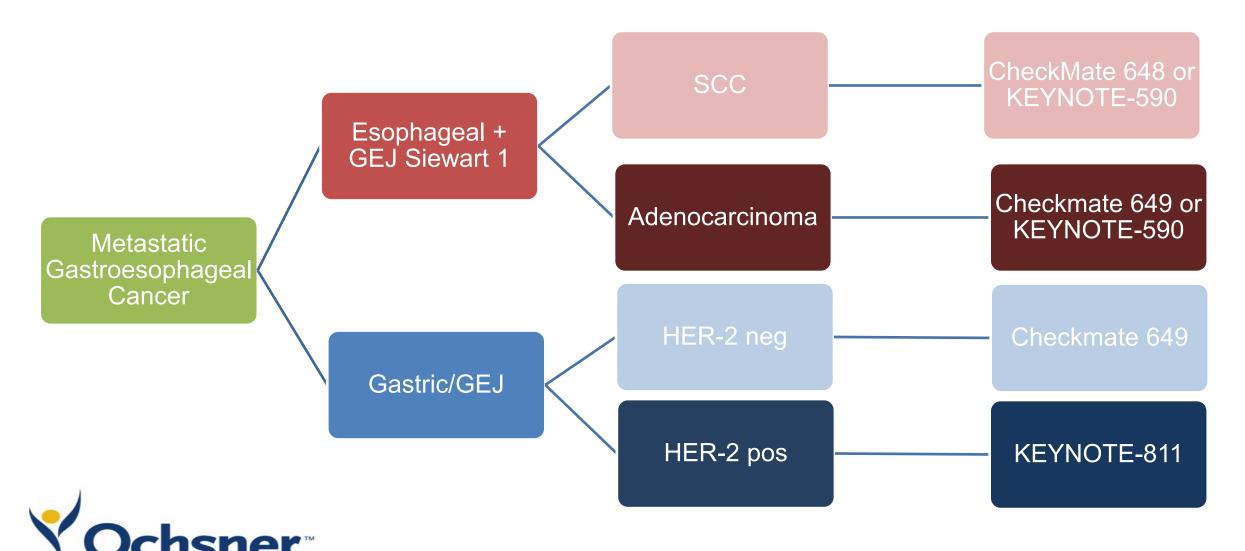






For visual learners...

Health System



Treatment - Metastatic

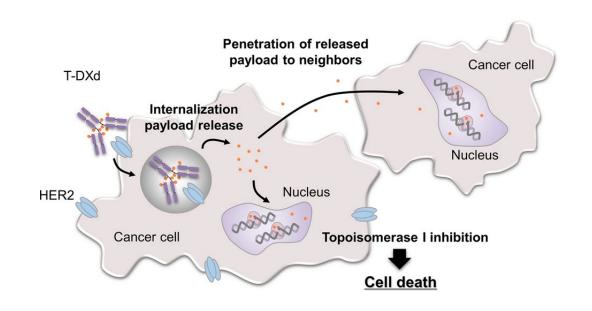
- 2nd + line options:
 - Paclitaxel +/- ramucirumab (adenocarcinoma)
 - Docetaxel
 - Irinotecan +/- 5-FU
 - Nivolumab (ESCC)
 - Trastuzumab deruxtecan (HER-2+)
 - TAS-102/Lonsurf



Pretreated HER-2 Positive Gastric Cancer

Trastuzumab Deruxtecan

- Antibody-drug conjugate
- HER-2 positive gastric cancer: DESTINY-Gastric01
- Randomized phase 2 study of HER-2
 positive patients that progressed on ≥ 2
 prior therapies including trastuzumab.
- ORR 51% in patients treated with trastuzumab deruxtecan vs 14% in control group.
- Median OS: 12.5 vs 8.4 months (P = 0.01)





Pretreated HER-2 Positive Gastric Cancer

- Trastuzumab Deruxtecan
 - Antibody-drug conjugate
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January 15, 2021

FDA approves fam-trastuzumab deruxtecan-nxki for HER2-positive gastric adenocarcinomas



Shitara et al. N Engl J Med 2020. Shitara et al Gastric Cancer 2021.

Gastroesophageal Cancer – FGFR2b overexpression

Bemarituzumab

- IgG1 monoclonal antibody to FGFR2b
- FIGHT trial: phase 2 trial of first-line HER-2 negative gastric cancer patients randomizing patients to FOLFOX +/- bemarituzumab
 - Patients must have FGFR2b overexpression or FGFR2 amplification by ctDNA
 - ⊙ 30% of prescreened patients met above criteria

TABLE 1: Outcomes From FIGHT Trial With Bemarituzumab Plus mFOLFOX6 vs Placebo

	Intent to Treat (n = 155)		IHC 2+/3+2	: 5% (n =118)	IHC 2+/3+≥10% (n = 96)		
	Bema	Placebo	Bema	Placebo	Berna	Bema	
mPFS	9.5 mo	7.4 mo	10.2 mo	7.3 mo	14.1 mo	7.3 mo	
	HR = 0.68		HR = 0.54		HR = 0.44		
mOS	NR	12.9 mo	NR	12.5 mo	NR	11.1 mo	
	HR =	0.58	HR =	0.52	HR =	0.41	

Berna = bernarituzumab; HR = hazard ratio; IHC = immunohistochemistry; mFOLFOX6 = modified fluorouracil, leucovorin, oxaliplatin; mOS = median overall survival; mPFS = median progression-free survival; NR = not reached.

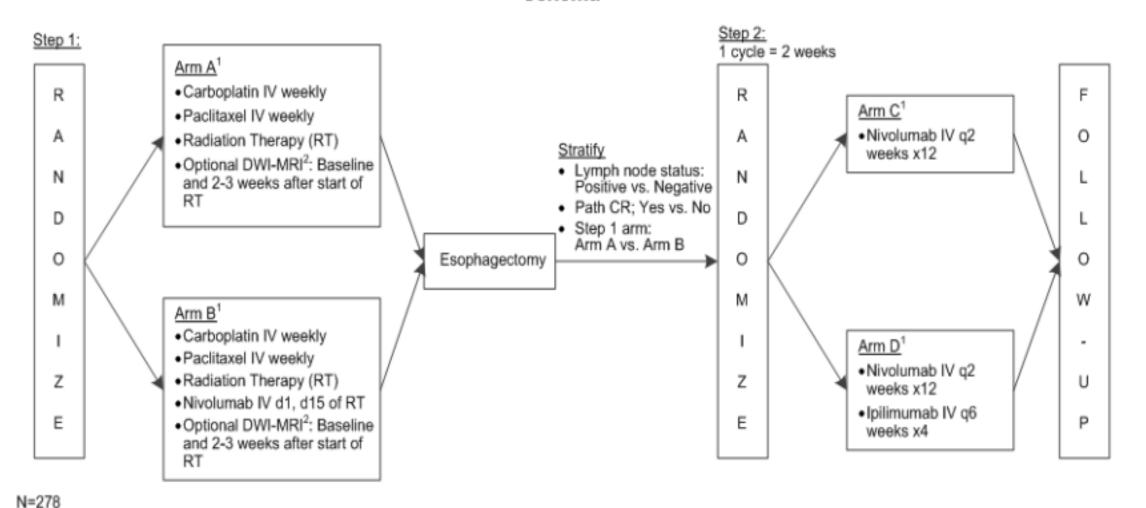


Future Directions

- Moving more targeted therapies into first line
 - Trastuzumab Deruxtecan for HER-2+
 - Bemarituzumab for FGFR2b +
 - Zolbetuximab for CLDN18.2 +
- Optimizing management of locally advanced disease
 - ESOPEC: FLOT vs CROSS regimen for esophageal and GEJ
 - Improving on KEYNOTE-577 EA2174
- Novel therapies
 - ADCs, BiTE, CAR-T



Schema





Summary and Take-Home Points

Localized Disease:

- FLOT is standard of care perioperative therapy for locally advanced gastric
- CROSS w/ adjuvant nivolumab is standard of care for locally advanced esophageal
- ESOPEC results should guide whether this will remain the case moving forward

Metastatic Disease:

- Immune checkpoint inhibitors nivolumab and pembrolizumab have made significant changes to first line therapy. Primarily driven by PD-L1 positive tumors.
- Targeted therapies HER-2 (KEYNOTE 811 in 1st line, DESTINY-Gastric01 in pre-treated) approved. FGFR2b, CLDN18.2 may be approved in the near future.
- Don't forget to check MMR/MSI status!
- All patients with advanced disease should have HER-2, MSI, PD-L1 status checked upfront.



Thanks! E-mail me with questions.

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