Gastrointestinal Oncology

Nataliya Uboha, MD, PhD, Associate Professor

University of Wisconsin, Carbone Cancer Center

Carbone Cancer Center

UNIVERSITY OF WISCONSIN

SCHOOL OF MEDICINE AND PUBLIC HEALTH

Disclosure of Conflicts of Interest

Nataliya Uboha, MD, PhD, has the following financial relationships to disclose:

- Consulting: QED, Taiho Inc., Incyte, AstraZeneca, Pfizer, Boston Gene, Helsinn.
- Research Funding: Taiho Inc, Ipsen, EMD Serono.
- Long position holdings: Natera, Exact Sciences.

Outline

- Biomarker Testing
- Immunotherapy Use
  - Pivotal Phase 3 Studies in Advanced Disease
  - Early-Stage Disease
  - MSI-High Tumors
- Targeting Her2 + GEA
- Emerging Biomarkers

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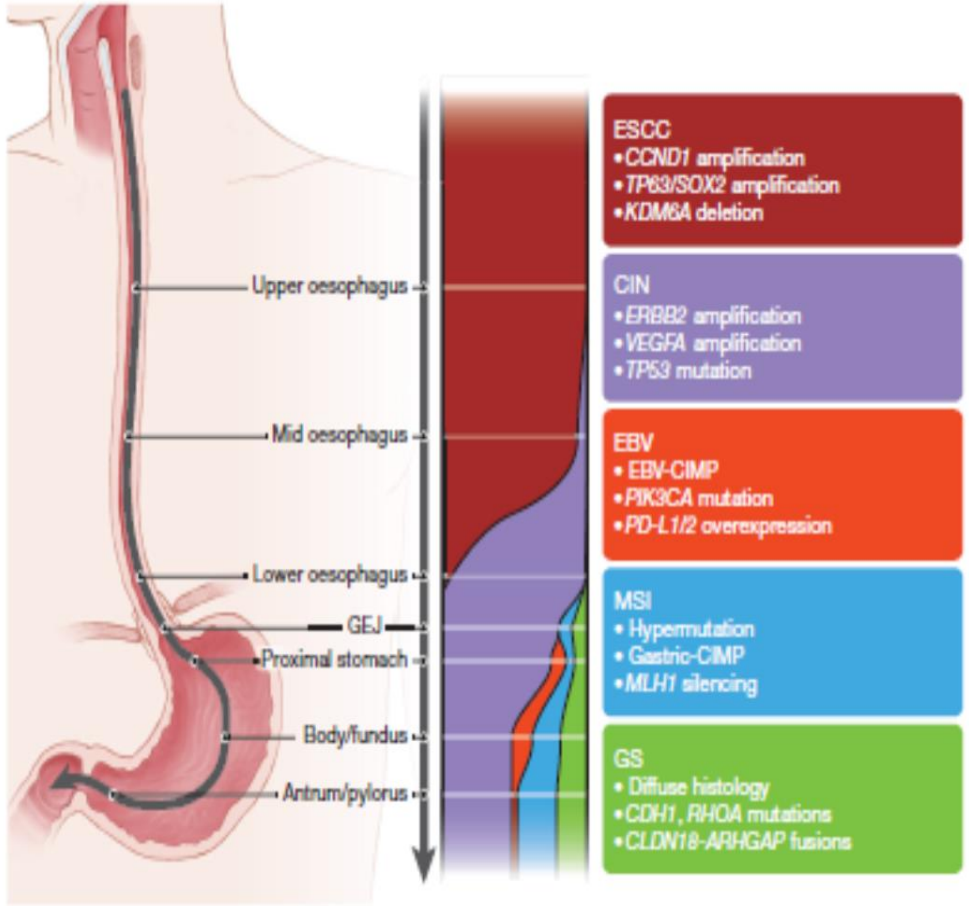
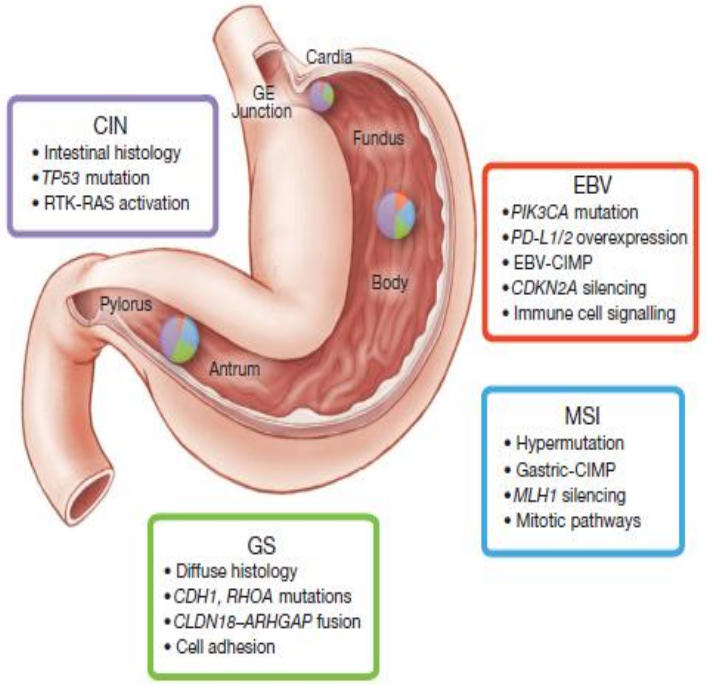
Anatomic & Molecular Heterogeneity



164 esophageal tumors, 359 gastric adenocarcinomas and 36 additional adenocarcinomas at the GEJ



EBV: Epstein Barr Virus; CIN: Chromosomal instability; GS: Genomically stable; MSI: Microsatellite unstable.

Nature 2017: 541, 169–175; Nature 2014 Sep 11;513(7517):202-9

Biomarkers in Upper GI Cancers

Current:

- PD-L1 expression
- Her-2 status (IHC and FISH as needed; NGS)
- Microsatellite status (PCR or IHC for MMR protein expression)
- Tumor Mutational Burden
- Next Generation Sequencing (NGS)

Under Investigation:

- Claudin 18.2, FGFR2b

PD-L1 Testing in Upper GI Tumors

PD-L1 tumor positive score (TPS):

% of viable tumor cells with partial or complete membrane staining in at least 100 viable tumor cells examined

PD-L1 combined positive score (CPS):

# of PD-L1-positive tumor cells, lymphocytes, and macrophages divided by the total number of viable tumor cells multiplied by 100; at least 100 viable tumor cells must be present.

PD-1 Antibodies:

Pembrolizumab	→ IHC 22C3 phamDx assay
Nivolumab	→ IHC 28-8 phamDx assay
Tislelizumab	→ IHC VENTANA SP263 assay

Challenges of PD-L1 Testing and Interpretation

Different antibodies across different studies:

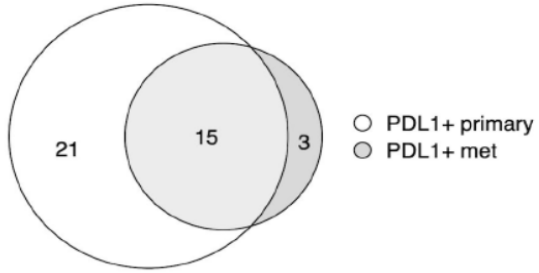
KEYNOTE-590 - Dako 22C3 CPS
CheckMate 648 - Dako 28-8 TPS
CheckMate 649 - Dako 28-8 CPS and TPS

Different cut-offs in different studies:

(CPS ≥1, 5, or 10%; TPS ≥1%)

Tumor Heterogeneity

PD-L1-status of paired **baseline primary and metastatic site**
61%, 38/62 concordance



		Baseline met PD-L1		
		Negative	Positive	Total
Baseline 1° PD-L1	Negative	23 (88%)	3 (12%)	26
	Positive	21 (58%)	15 (42%)	36
	Total	44 (71%)	18 (29%)	62

$p = 2.4 \times 10^{-4}$ by McNemar's test

Zhou KI et al. *Clin Cancer Res*. 2020;26(24):6453–6463

Adenocarcinoma vs. Squamous		
	TPS ≥1%	
Squamous	**49%**	Checkmate 648 (N = 970)
Adenocarcinoma	**16%**	Checkmate 649 (N = 1581)

Learning Curve
Adoption
Interpretation of results
Tissue availability

Outline

- Biomarker Testing
- **Immunotherapy Use**
  - **Pivotal Phase 3 Studies in Advanced Disease**
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- Targeting Her2 + GEA
- Emerging Biomarkers

Current Immunotherapy Approvals for HER2 Negative Esophagogastric Adenocarcinoma (EGA)

- **Nivolumab**: Locally advanced or metastatic EGA in combination with chemotherapy in first-line setting (*CheckMate 649*).
  - **FDA**: regardless of PD-L1 CPS
  - **NCCN**: PD-L1 CPS ≥5
- **Pembrolizumab**: Locally advanced or metastatic EGA in combination with chemotherapy in first-line setting (*Keynote 590*).
  - **FDA**: regardless of PD-L1 CPS
  - **NCCN**: PD-L1 CPS ≥10
- **NO** immunotherapy approvals **past first-line.**

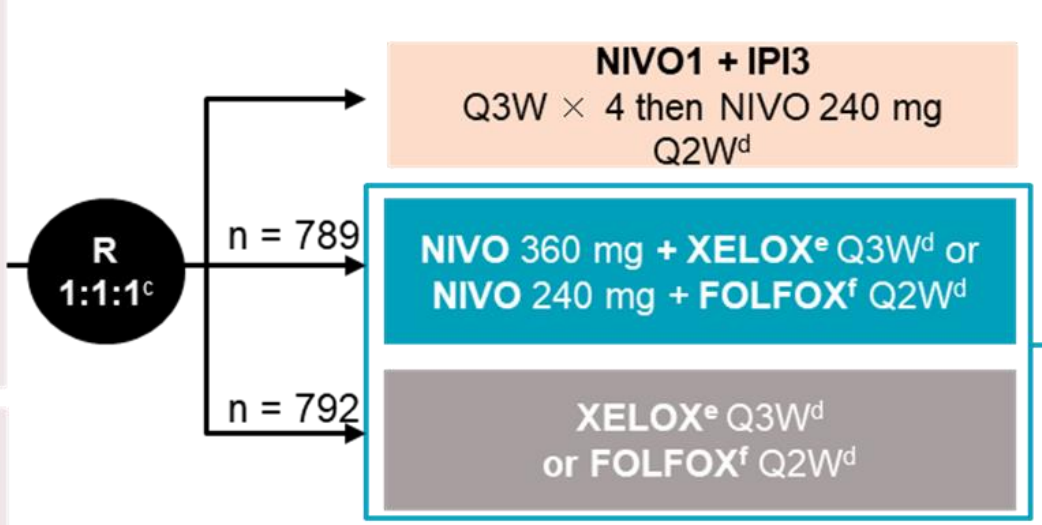
CheckMate 649: Phase 3 Global Study of Nivolumab & Chemo vs. Chemo in 1st Line EGA

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)



N = 1581, including 955 patients (60%) with PD-L1 CPS ≥ 5

Dual primary endpoints:

- **OS** and **PFS**[g] (PD-L1 CPS ≥ 5)

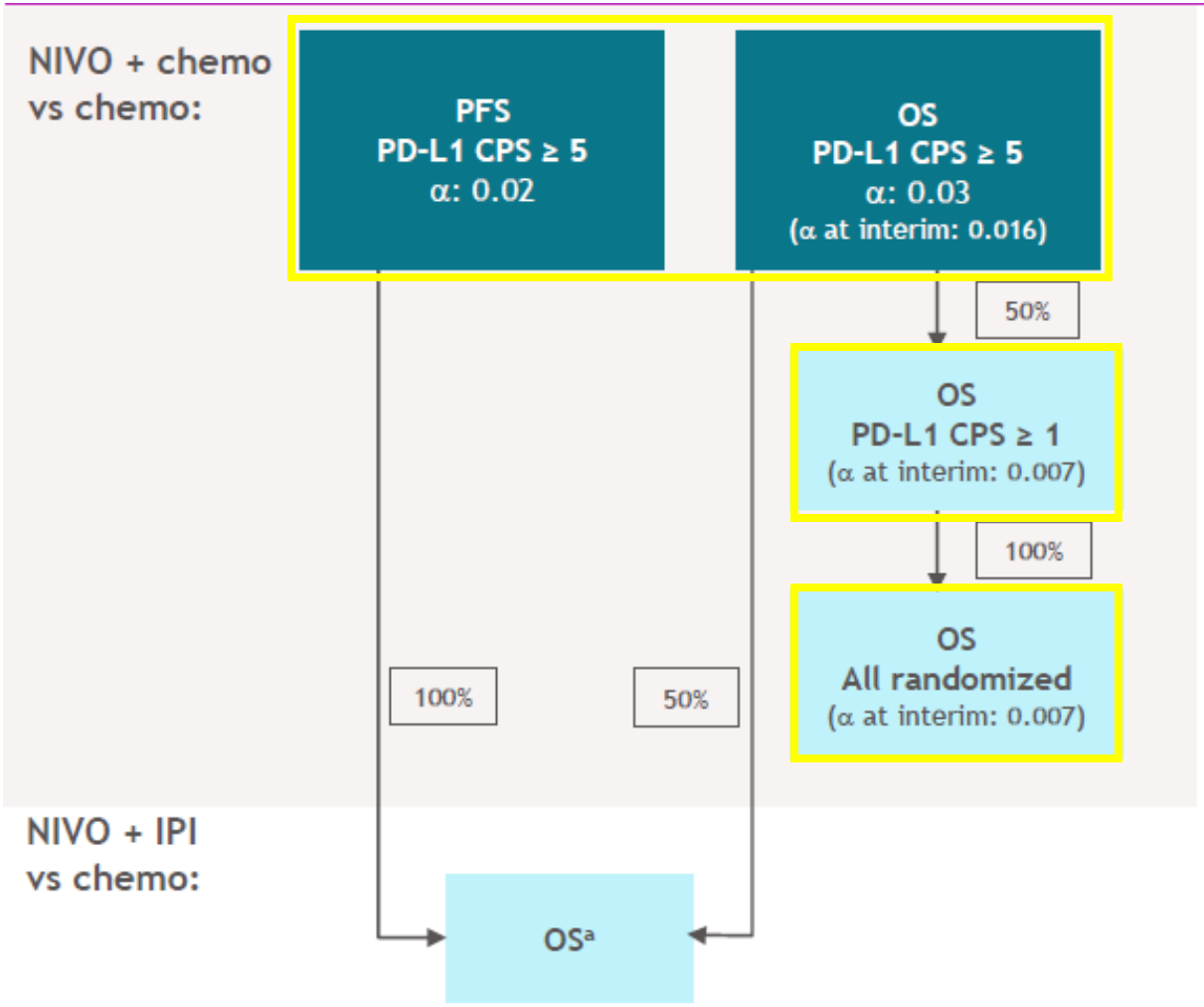
Secondary endpoints:

- **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]

[a]ClinicalTrials.gov number, NCT02872116; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed; [d]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1–14); [f]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1–2); [g]BICR assessed; [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

- Janjigian YY et al. *Lancet*. 2021;398(10294):27-40; Moehler M et al. ESMO 2020. Abstract LBA6.

CheckMate 649: Statistical Considerations



- Overall α is split between the 2 primary endpoints
- If OS in the PD-L1 CPS ≥ 5 population is statistically significant, OS in PD-L1 CPS ≥ 1, followed by OS in all randomized patients, is tested hierarchically
- Final PFS and pre-specified interim OS analyses: after a minimum follow-up of 12 months

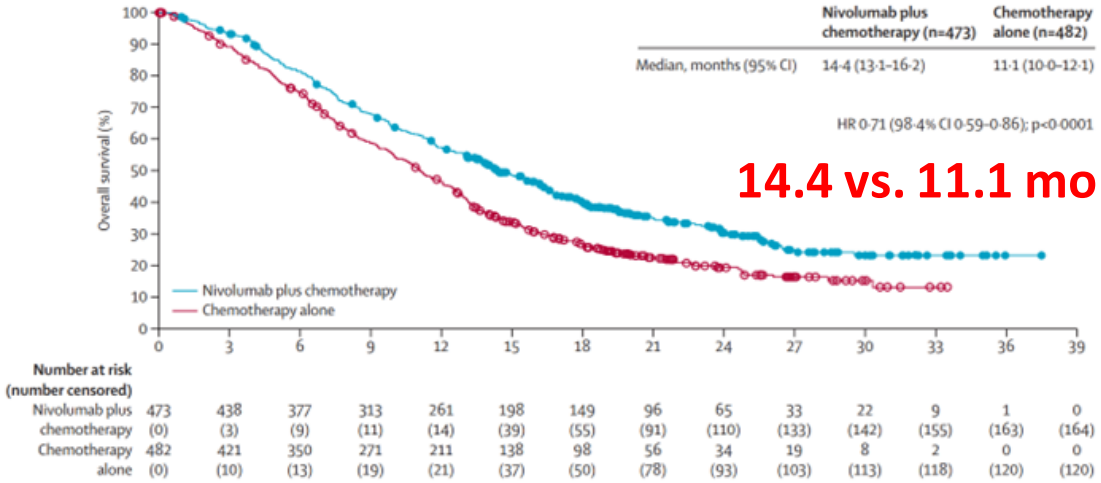
Primary endpoint
Secondary endpoint
% Fraction of α transmitted to next endpoint

[a]Hierarchical testing of OS in the PD-L1 CPS ≥ 5 population, followed by all randomized patients, is planned for the final analysis.

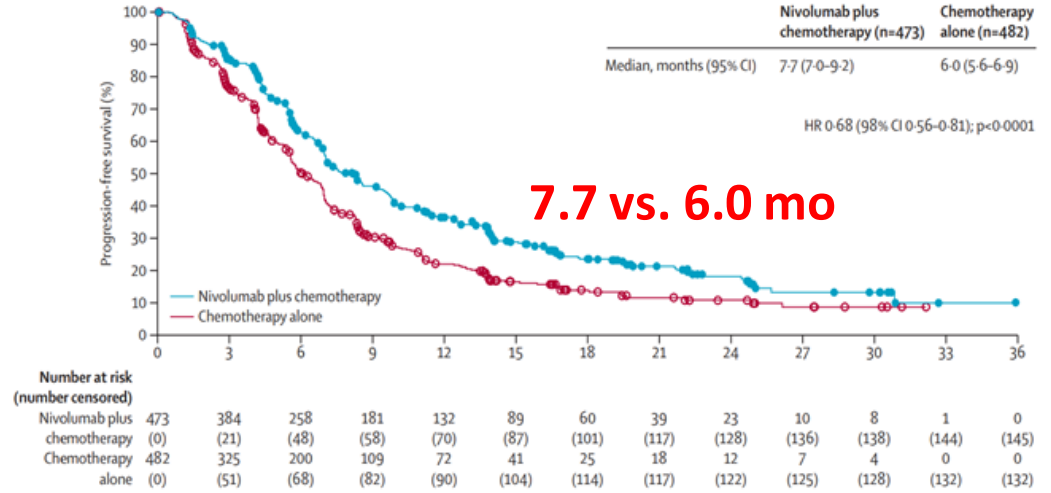
- Janjigian YY et al. *Lancet*. 2021;398(10294):27-40; Moehler M et al. ESMO 2020. Abstract LBA6.

Overall Survival and Progression Free Survival Results: CPS ≥5

Overall Survival



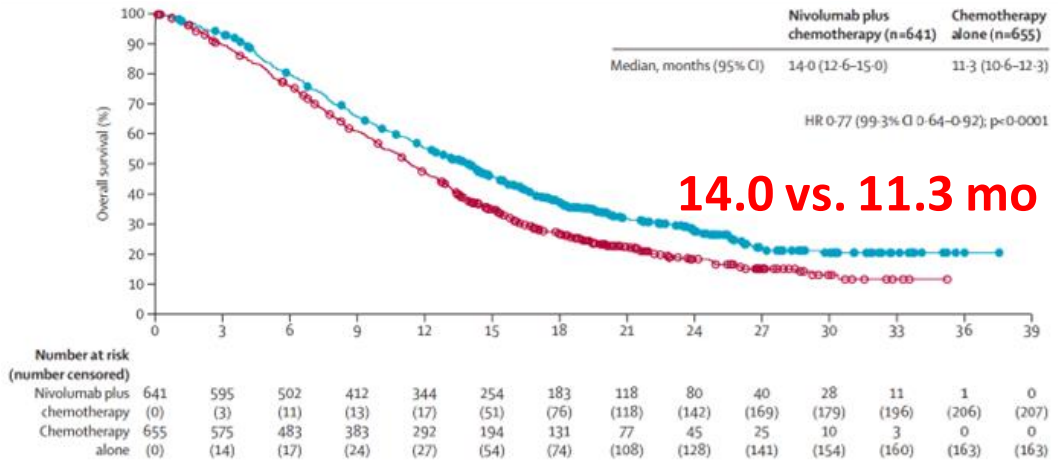
Progression Free Survival



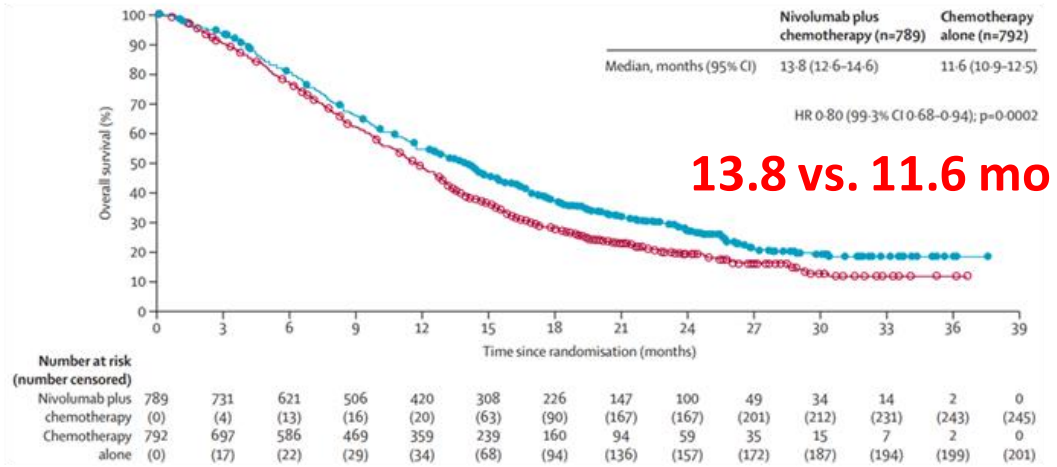
- Janjigian YY et al. *Lancet*. 2021;398(10294):27-40; Moehler M et al. ESMO 2020. Abstract LBA6.

Overall Survival Results: CPS ≥1 and All Randomized

CPS ≥ 1



All Randomized



- Janjigian YY et al. *Lancet*. 2021;398(10294):27-40; Moehler M et al. ESMO 2020. Abstract LBA6.

- Checkmate 649 met both primary endpoints and **ALL** *formally tested* secondary endpoints

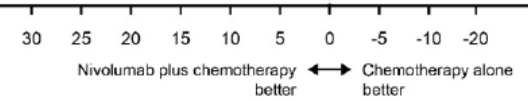
- 4/16/2021: FDA approved nivolumab + chemotherapy for **ALL** patients with advanced esophageal, GEJ, and gastric adenocarcinoma, regardless of PD-L1 expression

CheckMate 649: Subgroup Analyses

Population*	Median overall survival, months		Unstratified hazard ratio for death (95% CI)	Interaction test p value
	Nivolumab plus chemotherapy	Chemotherapy alone		
Overall (N=1581)	13·8	11·6	0·79 (0·70–0·89)	
PD-L1 CPS <1 (n=265)	13·1	12·5	0·92 (0·70–1·23)	
PD-L1 CPS ≥1 (n=1296)	14·0	11·3	0·76 (0·67–0·87)	0·2041
PD-L1 CPS <5 (n=606)	12·4	12·3	0·94 (0·78–1·13)	
PD-L1 CPS ≥5 (n=955)	14·4	11·1	0·70 (0·60–0·81)	0·0107†

Overall Survival

Population‡§	Objective response rate, %		Unweighted objective response rate difference,‖ % (95% CI)
	Nivolumab plus chemotherapy	Chemotherapy alone	
Overall (N=1211)	58	46	12 (6–17·5)
PD-L1 CPS <1 (n=178)	51	41	9 (–5 to 23)
PD-L1 CPS ≥1 (n=1019)	60	46	13 (7–19)
PD-L1 CPS <5 (n=428)	55	46	9 (–0·6 to 18)
PD-L1 CPS ≥5 (n=769)	60	45	15 (7·5–21)

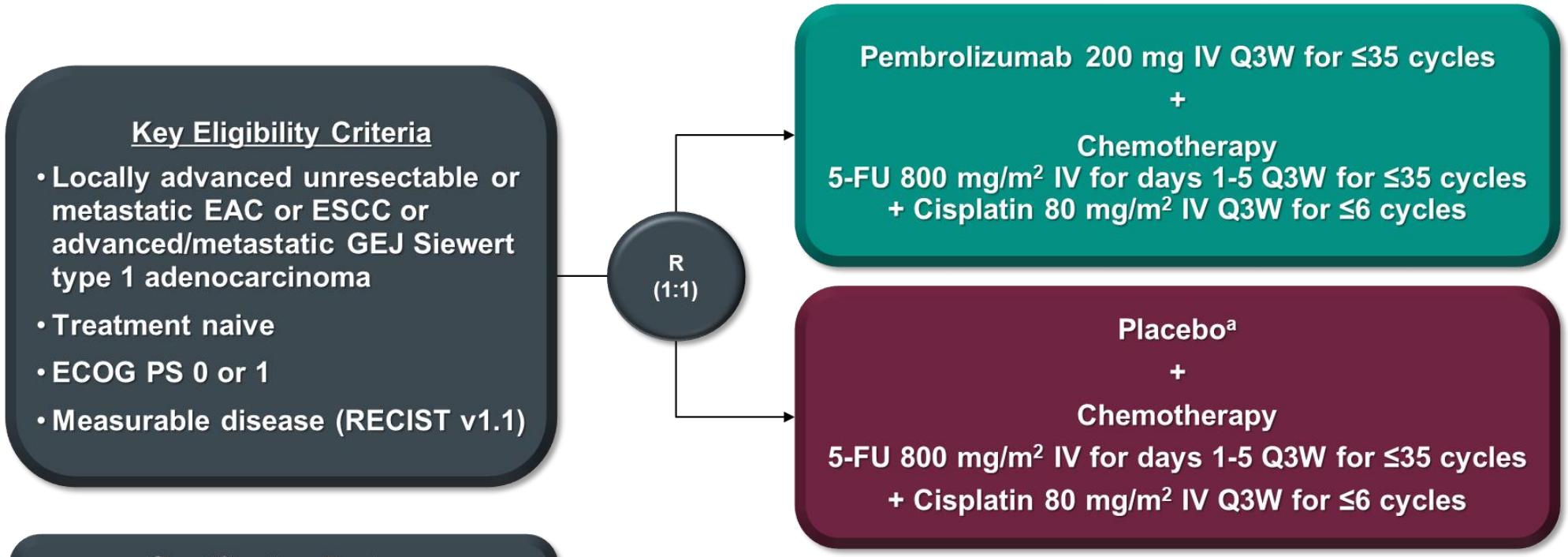


Objective Response Rate

NCCN category 1 recommendation:
Nivolumab should be reserved for those with PD-L1 CPS ≥ 5 tumors

Janjigian YY et al. *Lancet*. 2021;398(10294):27-40; Moehler M et al. ESMO 2020. Abstract LBA6.

KEYNOTE 590: Study Design (Esophageal and GEJ Study)



73% ESCC

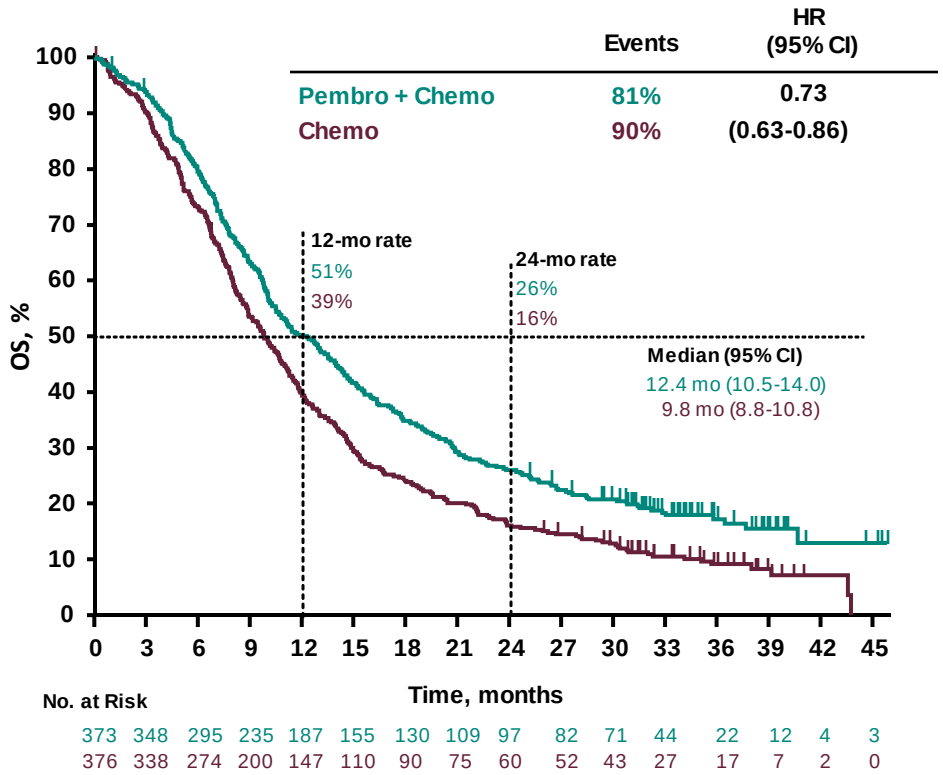
Pre-specified primary endpoints:

- OS in all pts, patients with ESCC PD-L1 CPS ≥10, ESCC, and PD-L1 CPS ≥10 tumors
- PFS (RECIST v1.1, investigator) in all patients, patients with ESCC, and PD-L1 CPS ≥10 tumors

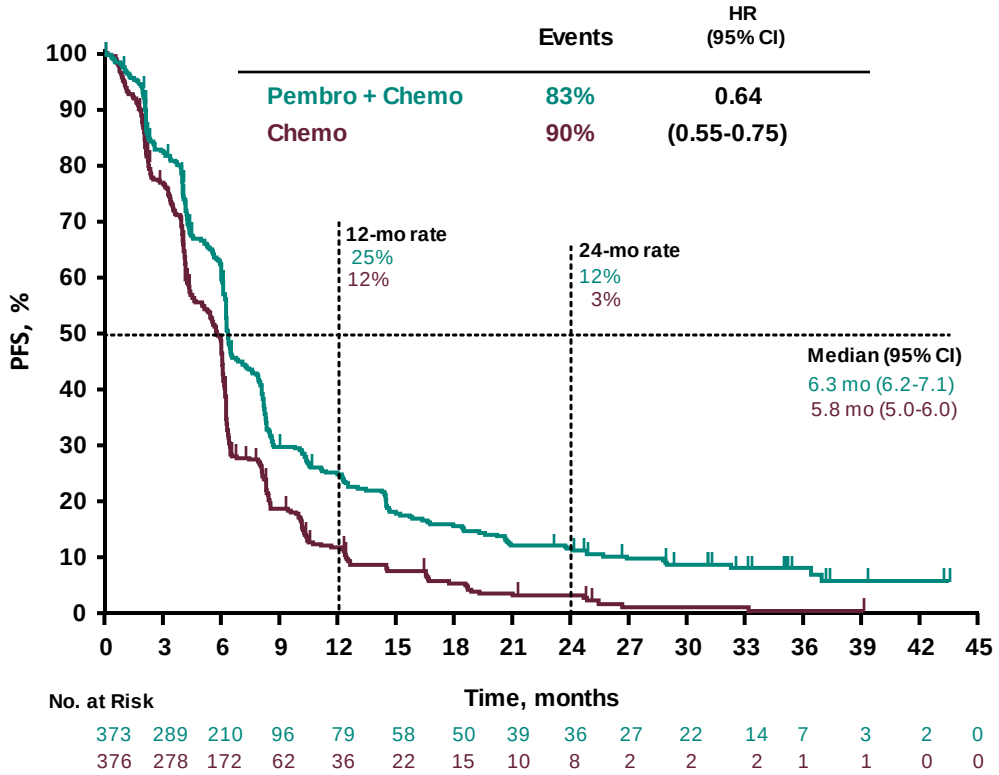
Sun et al, Lancet 2021 (398):759-71

KEYNOTE 590 OS and PFS: All Patients

Overall Survival



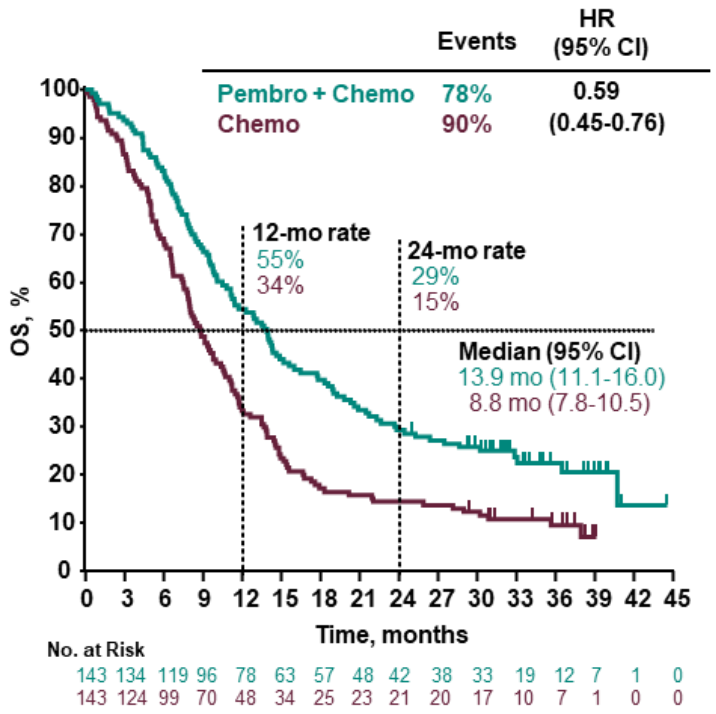
Progression Free Survival



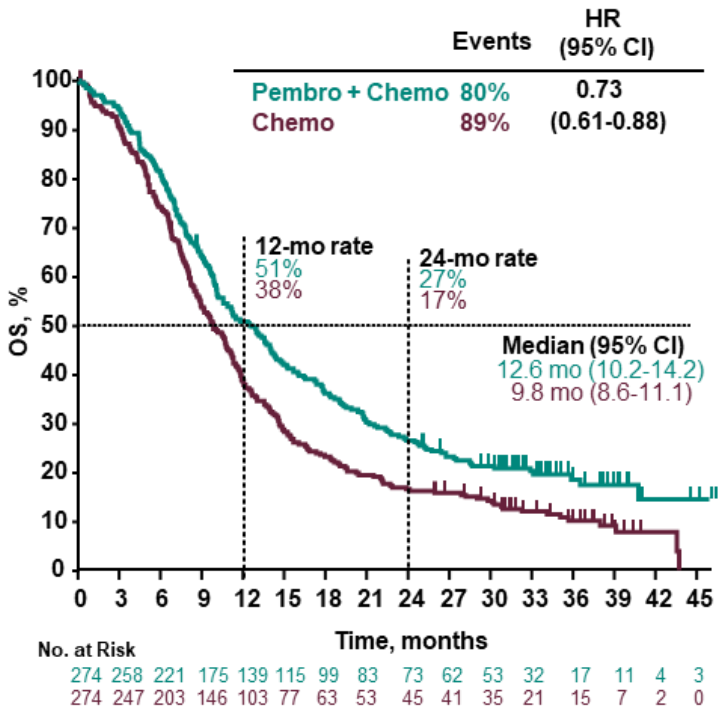
Sun et al, Lancet 2021 (398):759-71

KEYNOTE 590: OS in Pre-specified Subgroups

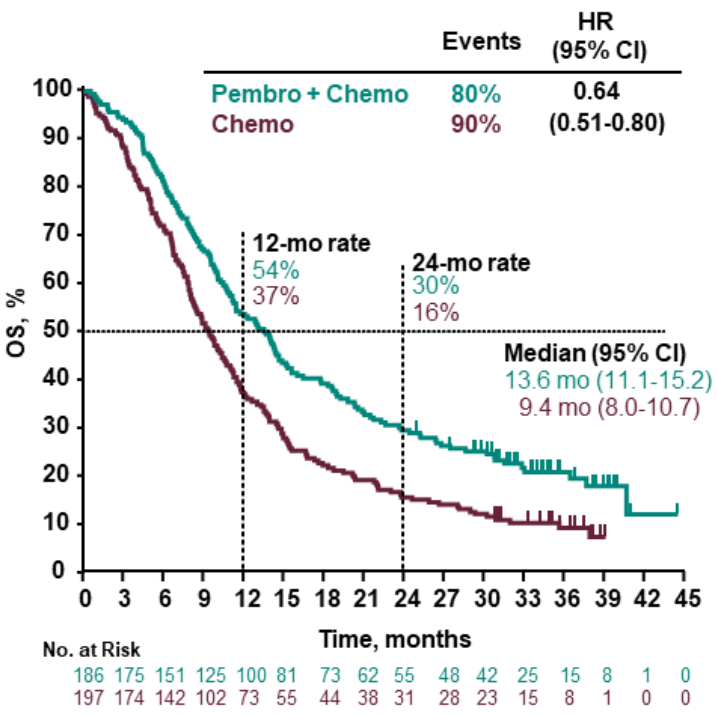
ESCC PD-L1 CPS ≥10



ESCC



PD-L1 CPS ≥10



Sun et al, Lancet 2021 (398):759-71

5/22/2021: FDA approved pembrolizumab + chemotherapy for patients with advanced esophageal and GEJ cancers, regardless of PD-L1 expression

BUT

It is more active against **PD-L1 +** Tumors

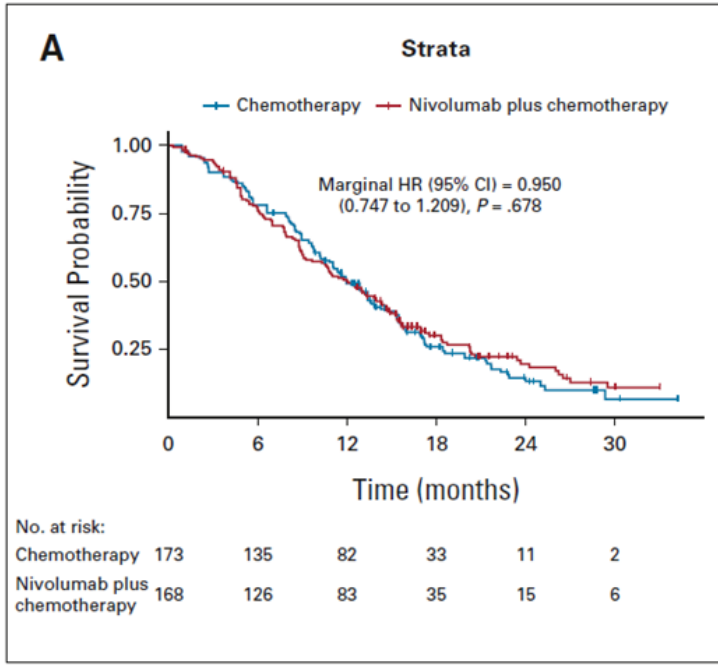
How Should We Approach Tumors with Low PD-L1 CPS?

Low Programmed Death-Ligand 1–Expressing Subgroup Outcomes of First-Line Immune Checkpoint Inhibitors in Gastric or Esophageal Adenocarcinoma

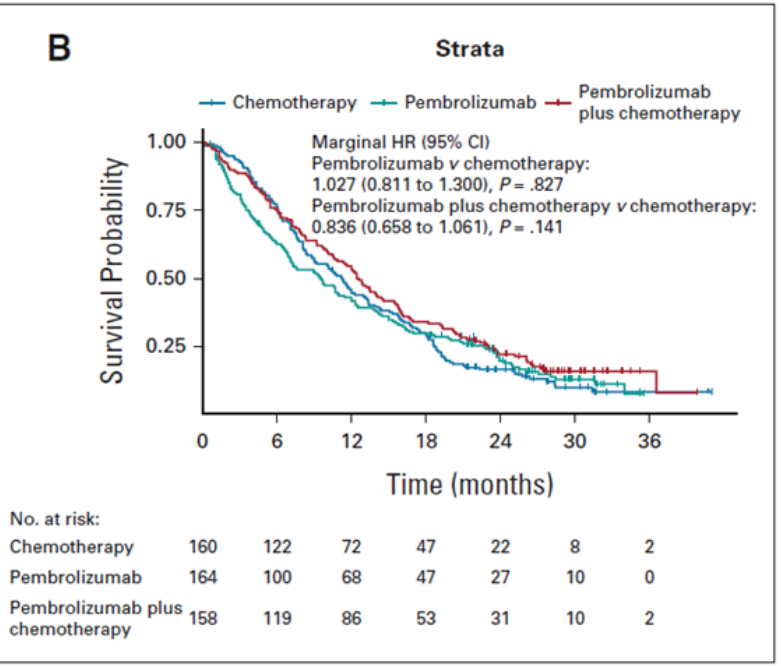
Joseph J. Zhao[1]; Dominic Wei Ting Yap[1]; Yiong Huak Chan, PhD[2]; Benjamin Kye Jyn Tan[1]; Chong Boon Teo[1]; Nicholas L. Syn, MBBS[1]; Elizabeth C. Smyth, MD[3]; Yu Yang Soon, MBBS (Hons)[4]; and Raghav Sundar, MBBS, PhD[1,5,6,7,8]

NO ACTIVITY OF IO AGENTS

CheckMate-649 PD-L1 CPS 1-4



KEYNOTE-062 PD-L1 CPS 1-9



Zhao et al, Journal of Clinical Oncology 2021(40):392-402

Single-Agent Anti-PD1/PD-L1 in EGA in Later Lines

3rd Line+		OS	ORR	ORR in PDL1+
Attraction-2	Nivo vs. Placebo	5.26 vs. 4.14 mo*	**11.2%**	Benefit regardless of PD-L1 status (TPS)
Keynote-059	Pembro	5.6 mo	**11.6%**	**15.5%** in CPS ≥1
Javelin 300	Avelumab vs. Chemo	4.6 vs. 5.0 mo	**2.2%**	**4.3%** in TPS ≥1
2nd Line		**OS**	**ORR**	**ORR in PDL1+**
Keynote 181**	Pembro vs. chemo	6.3 vs 6.9 mo***	**3.3%** in PD-L1 CPS <10	**18%** in PD-L1 CPS ≥10
Keynote 061	Pembro vs. paclitaxel	9.1 vs. 8.3 mo	**16%** In CPS ≥1	**24%** in PD-L1 CPS ≥10

** Statistically significant difference; ** Data for adenocarcinoma, PDL1 CPS ≥ 10; *** PDL1 CPS ≥ 10 tumors*

Limited Activity
Higher responses in PDL1 + tumors
But results are largely irrelevant since studies enrolled IO naive patients

Chen L-T et al. *Gastric Cancer.* 2020;23(3):510-519; Fuchs CS et al. *JAMA Oncol.* 2018;4(5):e180013; Bang Y-J et al. *Ann Oncol.* 2018;29(10):2052-2060; Fuchs CS et al. ASCO 2020. Abstract 4503.

Immunotherapy for Advanced EGA

	Regimen	Biomarker Selection	Study
1st line	Pembrolizumab plus chemotherapy (preferably with cisplatin) for E/GEJ	Definitely for PD-L1 CPS ≥10 *FDA approved for all*	KEYNOTE-590
	Nivolumab plus chemotherapy	Definitely for PD-L1 CPS≥5 No benefit for PD-L1 CPS < 5 *FDA approved for all*	CheckMate 649
2nd line+	No approved IO agents	Not applicable	KEYNOTE-181 KEYNOTE-061 Javelin 300

Current Immunotherapy Approvals for ESCC

- **Pembrolizumab:**

  - Locally advanced or metastatic SCC in combination with chemotherapy in first-line setting (*Keynote 590*)

  - Advanced ESCC with PD-L1 CPS ≥10 with disease progression after one or more prior lines of systemic therapy (*Keynote-181*)

- **Nivolumab:**

  - Locally advanced or metastatic SCC in combination with chemotherapy in first-line setting (*Checkmate 648*)

  - Advanced ESCC after prior fluoropyrimidine- and platinum-based chemotherapy(*Attraction-3*)

- **Ipilimumab:**

  - Locally advanced or metastatic combination with **nivolumab** in first-line setting (*Checkmate 648*)

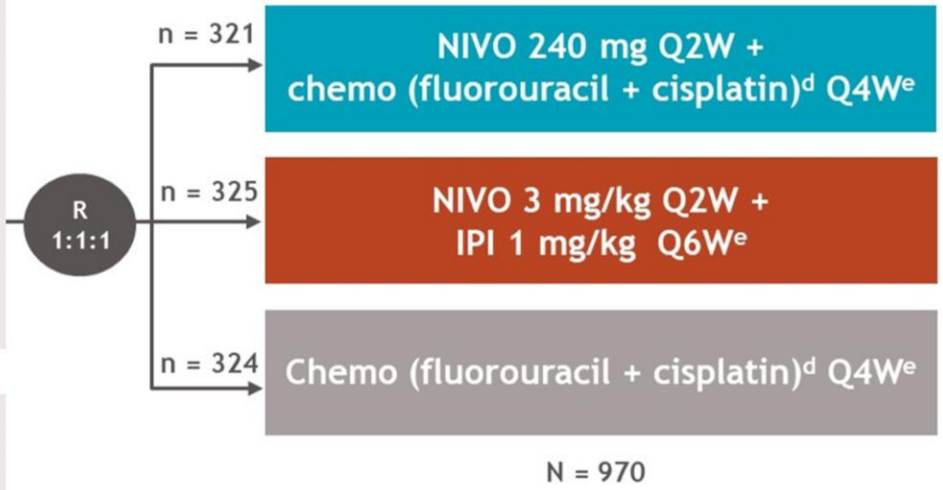
Current Immunotherapy Approvals for ESCC

- **Pembrolizumab:**
  - Locally advanced or metastatic SCC in combination with chemotherapy in first-line setting (*Keynote 590*)
  - Advanced ESCC with PD-L1 CPS ≥10 with disease progression after one or more prior lines of systemic therapy (*Keynote-181*)
- **Nivolumab:**
  - Locally advanced or metastatic SCC in combination with chemotherapy in first-line setting (*Checkmate 648*)
  - Advanced ESCC after prior fluoropyrimidine- and platinum-based chemotherapy(*Attraction-3*)
- **Ipilimumab:**
  - Locally advanced or metastatic combination with **nivolumab** in first-line setting (*Checkmate 648*)

CheckMate 648: Phase 3 Global Study of Nivolumab & Chemo vs. Nivolumab & Ipilimumab vs. Chemo in 1st Line ESCC

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 months[g]

[a]ClinicalTrials.gov. NCT03143153; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]East Asia includes patients from Japan, Korea, and Taiwan; [d]Fluorouracil 800 mg/m^2 IV daily (days 1-5) and cisplatin 80 mg/m^2 IV (day 1); [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years; [f]Per blinded independent central review (BICR); [g]Time from last patient randomized to clinical data cutoff.

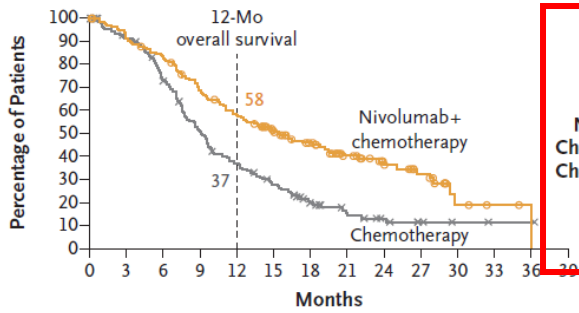
Doki et al, N Engl J Med 2022 Vol. 386 Issue 5 Pages 449-46

CheckMate 648: Efficacy Results

Chemo+ Nivo vs. Chemo

PDL1 TPS ≥1%

A Overall Survival in Patients with Tumor-Cell PD-L1 Expression of ≥1%



	No. of Patients	Median Overall Survival (95% CI) mo
Nivolumab+ Chemotherapy	158	15.4 (11.9–19.5)
Chemotherapy	157	9.1 (7.7–10.0)

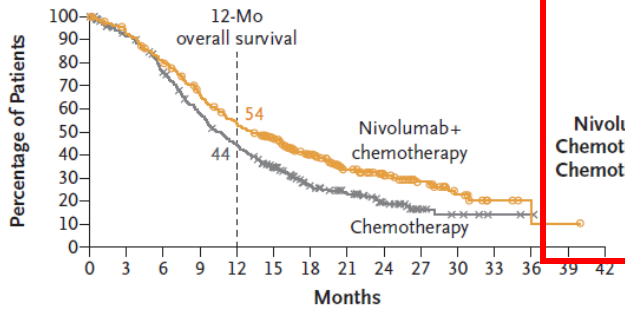
Hazard ratio for death, 0.54 (99.5% CI, 0.37–0.80)
P<0.001

No. at Risk

Nivolumab+chemotherapy	158	143	129	105	88	70	53	36	22	16	4	2	0	0
Chemotherapy	157	135	105	72	52	36	21	12	8	4	2	1	1	0

ALL Patients

B Overall Survival in the Overall Population



	No. of Patients	Median Overall Survival (95% CI) mo
Nivolumab+ Chemotherapy	321	13.2 (11.1–15.7)
Chemotherapy	324	10.7 (9.4–11.9)

Hazard ratio for death, 0.74 (99.1% CI, 0.58–0.96)
P=0.002

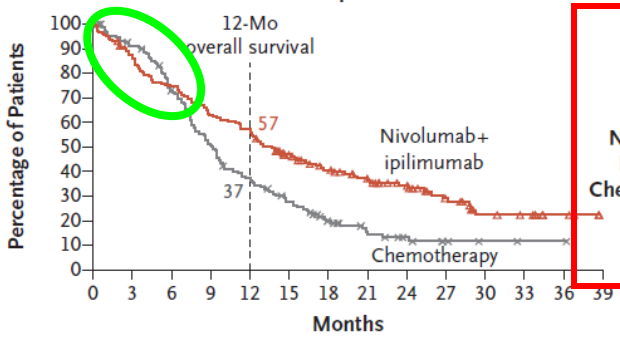
No. at Risk

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

Ipi + Nivo vs. Chemo

PDL1 TPS ≥1%

A Overall Survival in Patients with Tumor-Cell PD-L1 Expression of ≥1%



	No. of Patients	Median Overall Survival (95% CI) mo
Nivolumab+ Ipilimumab	158	13.7 (11.2–17.0)
Chemotherapy	157	9.1 (7.7–10.0)

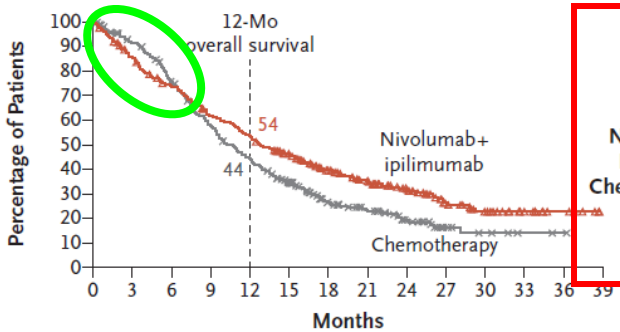
Hazard ratio for death, 0.64 (98.6% CI, 0.46–0.90)
P=0.001

No. at Risk

Nivolumab+ipilimumab	158	136	116	98	89	63	50	40	31	20	11	9	4	0
Chemotherapy	157	135	105	72	52	36	21	12	8	4	2	1	1	0

ALL Patients

B Overall Survival in the Overall Population



	No. of Patients	Median Overall Survival (95% CI) mo
Nivolumab+ Ipilimumab	325	12.7 (11.3–15.5)
Chemotherapy	324	10.7 (9.4–11.9)

Hazard ratio for death, 0.78 (98.2% CI, 0.62–0.98)
P=0.01

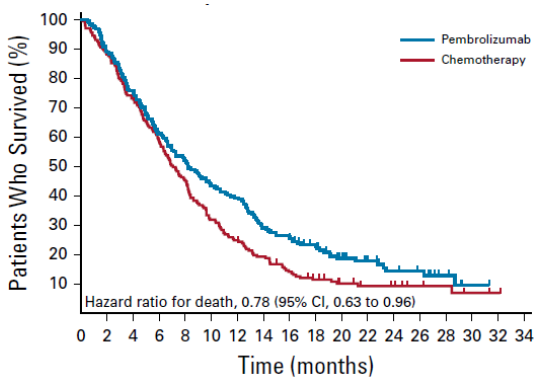
No. at Risk

Nivolumab+ipilimumab	325	274	232	191	166	129	97	77	55	33	22	12	6	0
Chemotherapy	324	281	229	171	131	93	56	41	23	9	5	2	1	0

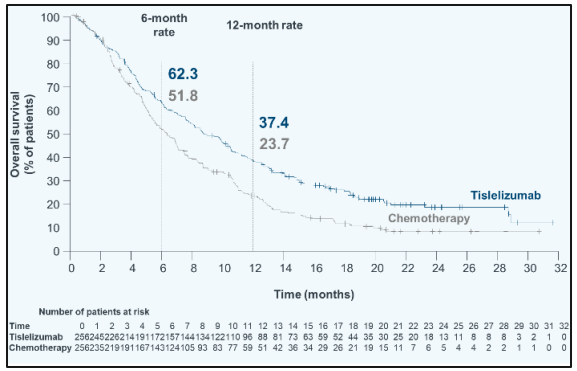
Doki et al, N Engl J Med 2022 Vol. 386 Issue 5 Pages 449-46

Select Phase 3 Studies with IO Agents in Later Lines in Advanced ESCC

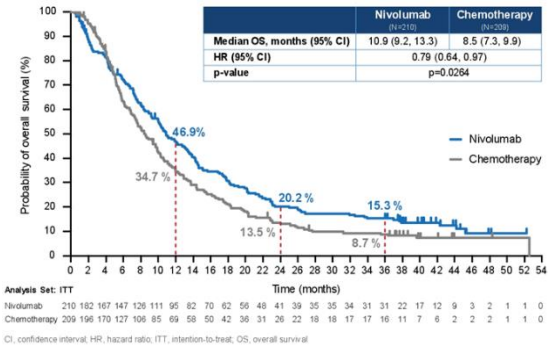
KEYNOTE 181: Pembro improves OS vs. chemo in ESCC with PD-L1 ≥10 and trend toward better OS in all ESCC



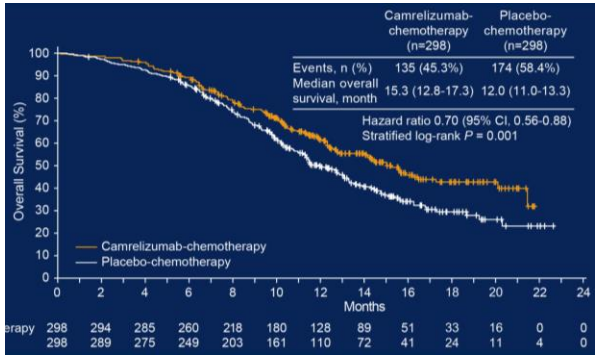
RATIONALE 302: Tislelizumab improves OS vs chemo



ATTRACTION 3: Nivolumab improves OS compared to chemo in ESCC



ESCORT-1: Camrelizumab improves OS compared to chemo in ESCC



However, patients were *immunotherapy naïve* in these studies.
As such, these results are largely irrelevant when IO agents are used in 1st line setting.

Kato K et al. *Lancet Oncol.* 2019;20(11):1506-1517; Shen L et al. ASCO 2021. Abstract 4012; Chin K et al. ASCO GI 2021. Abstract 204.

Approach to Advanced ESCC

	Therapy	Biomarker Selection	Study
1st line	Pembrolizumab plus chemotherapy	Definitely for PD-L1 CPS ≥10 *FDA approved for all*	KEYNOTE-590
	Nivolumab plus chemotherapy	None Higher activity in PDL1 TPS >1%	CheckMate 648
	Nivolumab plus ipilimumab (if not a chemotherapy candidate)	None Higher activity in PDL1 TPS >1%	CheckMate 648
2nd line+	Nivolumab	None *(No prior IO therapy)*	ATTRACTION-3
	Pembrolizumab	PD-L1 CPS ≥ 10 *(No prior IO therapy)*	KEYNOTE-181

Outline

- Biomarker Testing
- **Immunotherapy Use**
  - Pivotal Phase 3 Studies in Advanced Disease
  - **Early-Stage Disease**
  - MSI-High Tumors
- Targeting Her2 + GEA
- Emerging Biomarkers

Adjuvant Nivolumab Tackles Systemic Recurrences

CheckMate 577: Study Design

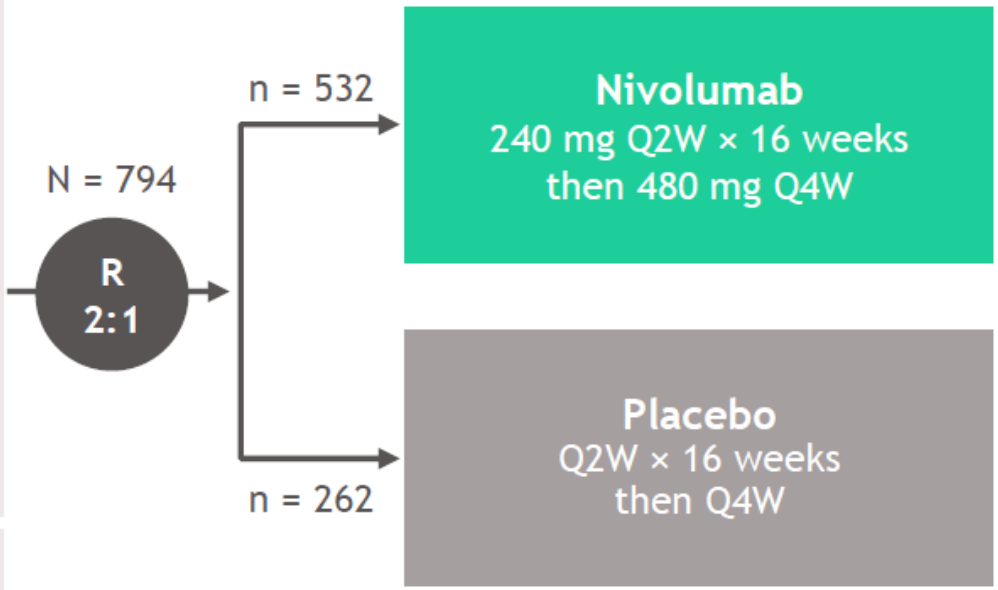
- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

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])



Primary endpoint:

- DFS[e]

Secondary endpoints:

- OS[f]
- OS rate at 1, 2, and 3 years

29% SCC
72% PDL1 TPS <1%

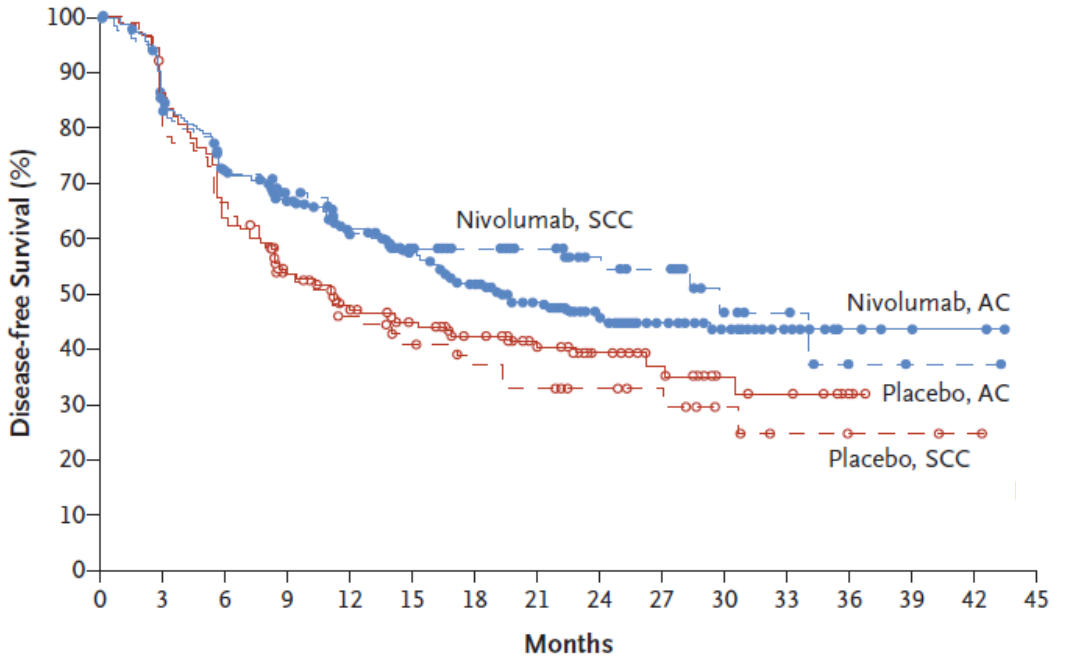
Total treatment duration of up to 1 year[d]

- 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%)

Kelly et al, NEJM 2021 (384): 1191-203

Adjuvant Nivolumab Prolongs Disease Free Survival

Disease Free Survival by Histology



	Nivolumab N=155	Placebo N=75
Median DFS	22.4 mo	11.0 mo
Median DFS SCC	29.7 mo	11.1 mo
	HR 0.61 (95% CI, 0.42-0.88)	

Treatment Related Adverse Events

	Nivolumab	Placebo
AEs Leading to treatment discontinuation	9%	3%
Serious adverse events	8%	3%
Any grade ≥3 TRAE	13%	6%
Grade ≥3 fatigue	1%	<1%

5/20/2021: FDA approves 1 year of adjuvant nivolumab for patients with residual disease at resection post chemoRT.

Kelly et al, NEJM 2021 (384): 1191-203

Ongoing Select IO Trials for Early-Stage Upper GI Cancers

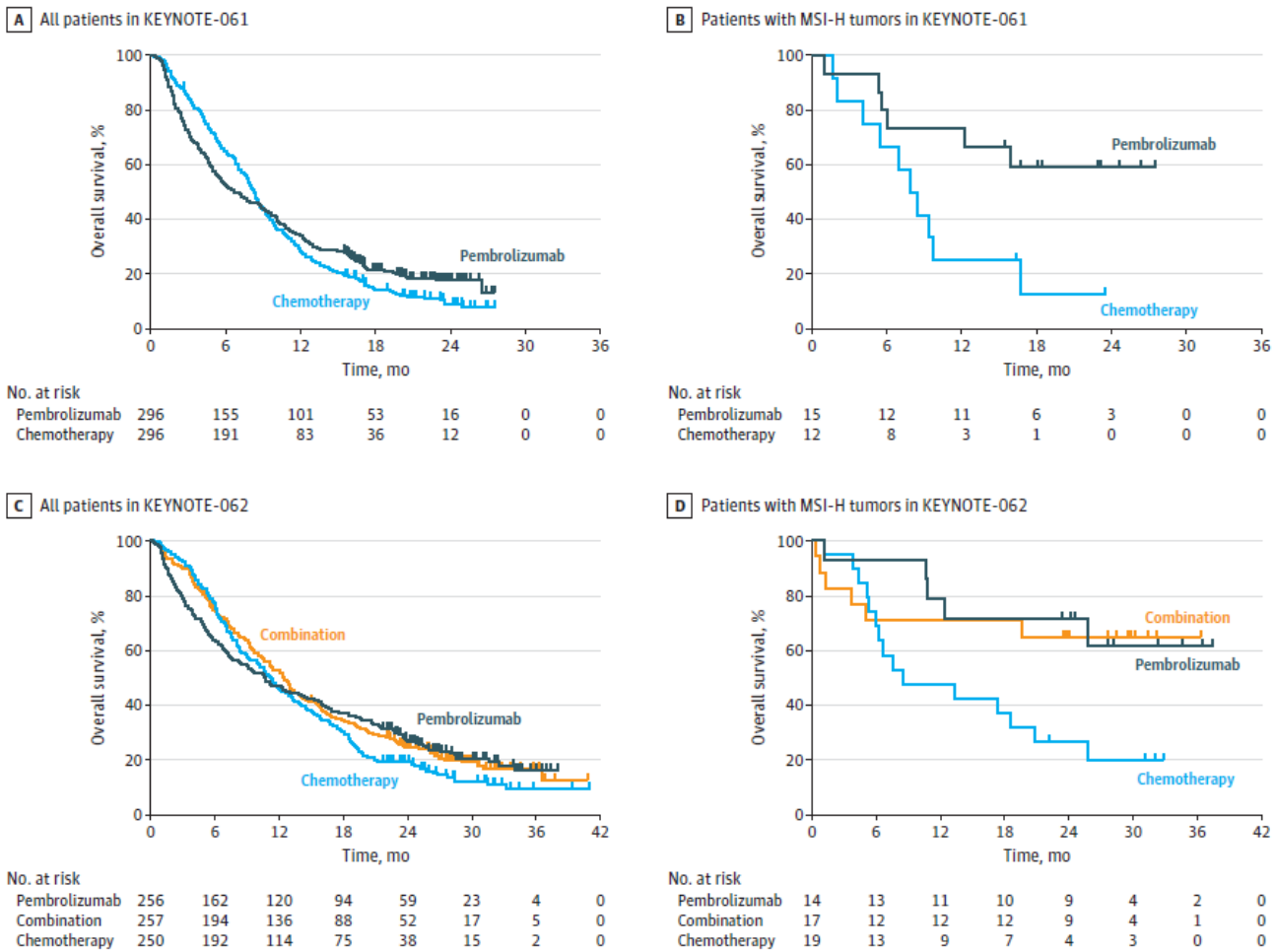
Study Name and/or Number	Study Design	Planned # of Patients	Geography
KEYNOTE 585 **NCT03221426**	Double-blind study of perioperative **pembrolizumab vs. placebo plus chemotherapy** in resectable gastric and GEJ adenocarcinoma	1007	Global
MATTERHORN **NCT04592913**	Double-blind, placebo-controlled study of perioperative **FLOT chemotherapy with durvalumab vs. placebo** in resectable gastric or GEJ adenocarcinoma	900	Global
KEYNOTE-975 **NCT04210115**	Double-blind, placebo-controlled study of **pembrolizumab vs. placebo in esophageal carcinoma treated with definitive chemoradiation**	600	Global
EA2174 **NCT03604991**	Peri-operative **Nivolumab and Ipilimumab** in patients with locoregional esophageal and gastroesophageal junction adenocarcinoma treated with **neoadjuvant chemoradiation**	278	USA
SKYSCRAPER-07 **NCT04543617**	Double-blind, placebo-controlled study of **atezolizumab with or without tiragolumab (anti-TIGIT antibody) vs. placebo in unresectable ESCC** after definitive chemoradiation	750	GLobal

Outline

- Biomarker Testing
- **Immunotherapy Use**
  - Pivotal Phase 3 Studies in Advanced Disease
  - Early Stage Disease
  - **MSI-High Tumors**
- Targeting Her2 + GEA
- Emerging Biomarker

JAMA Oncology | Brief Report

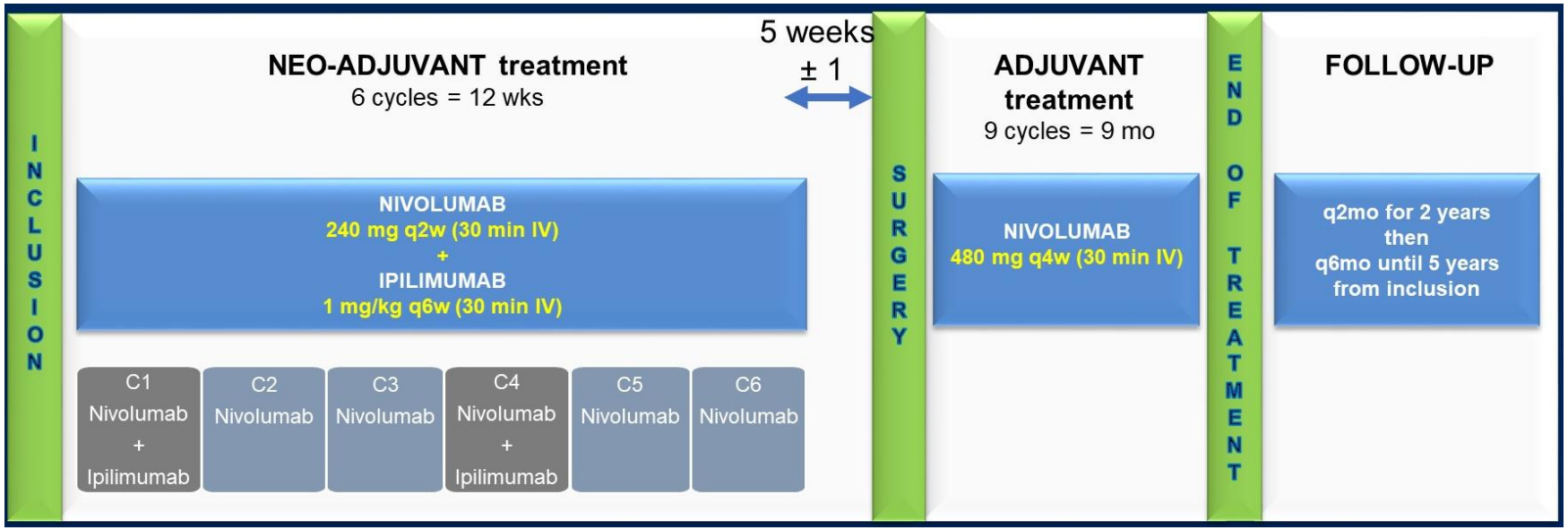
Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability–High Gastric or Gastroesophageal Junction Cancer Among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials



Chao et al, JAMA Oncol. 2021;7(6):895-902

NEONIPIGA: Study Design

Patients with resectable MSI-H/dMMR EGA cT2-T4, Nx, Mo

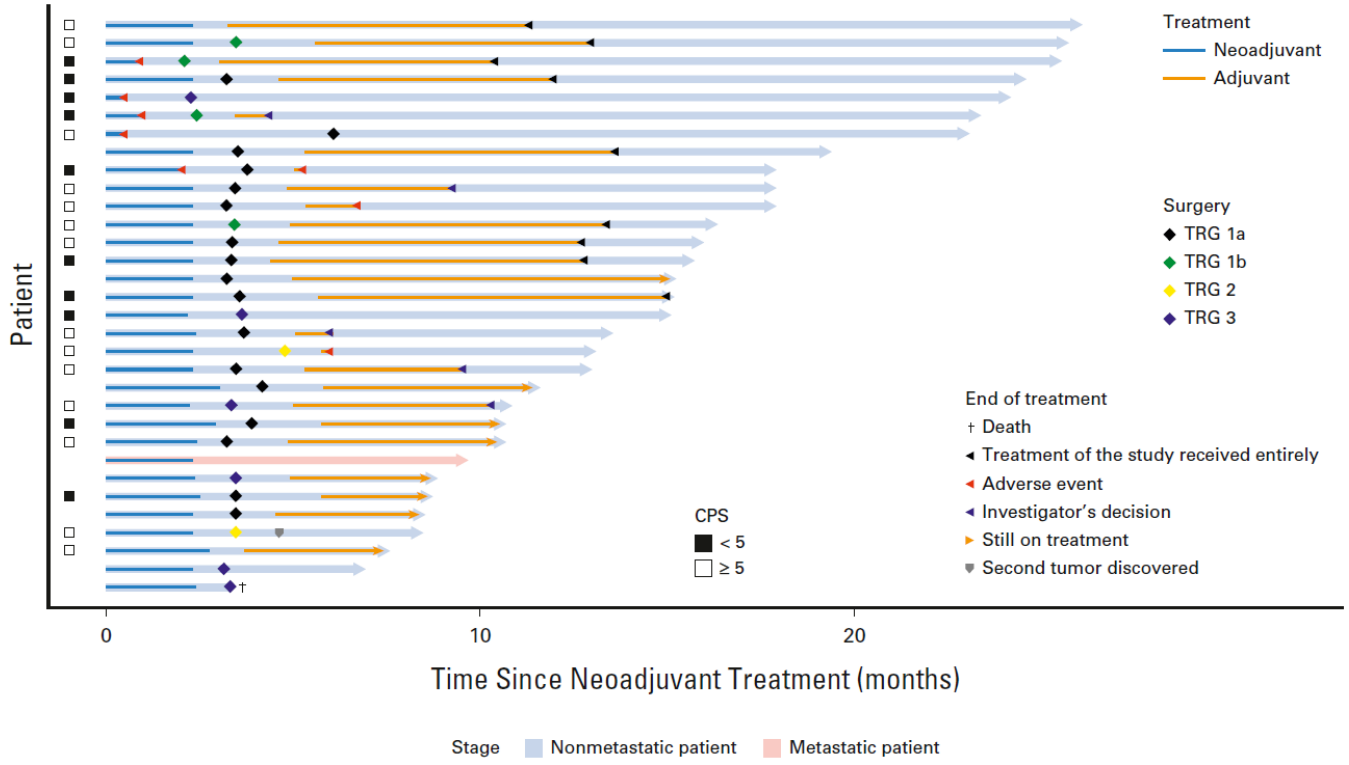


Primary endpoint: path CR Rate

Presented by Thierry Andre et al, GI ASCO 2022

Pathological Outcomes

Characteristic	Patients (n = 29), No. (%)
TRG Becker	
TRG 1a: complete tumor regression without residual tumor	17 (59)
TRG 1b: < 10% residual tumor per tumor bed	4 (14)[a]
TGR 2: 10% to 50% residual tumor	2 (7)
TRG 3: > 50% residual tumor cells	6 (21)



Andre et al, JCO 2022; https://doi.org/10.1200/JCO.22.00686

Remaining Questions about MSI-H/dMMR Tumors

- Can we move IO into first line and omit chemotherapy in the treatment of advanced disease?

- Can we omit chemotherapy, radiation and/or surgery in the treatment of early stage disease?

Outline

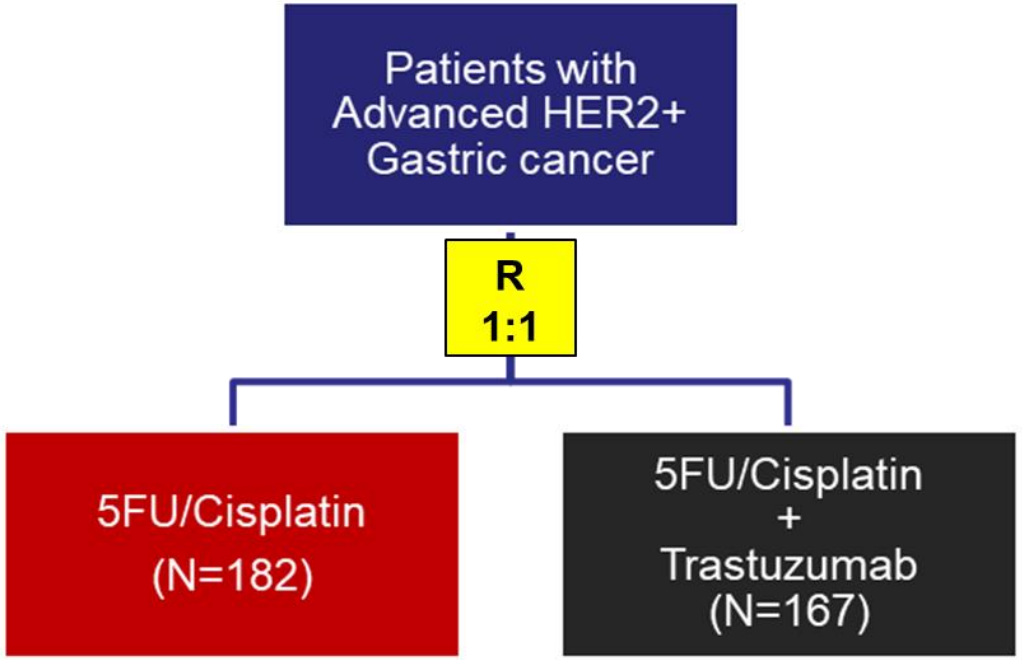
- Biomarker Testing
- Immunotherapy Use
  - Pivotal Phase 3 Studies in Advanced Disease
  - Early Stage Disease
  - MSI-High Tumors
- **Targeting Her2 + GEA**
- Emerging Biomarkers

HER2+ Upper GI Adenocarcinomas

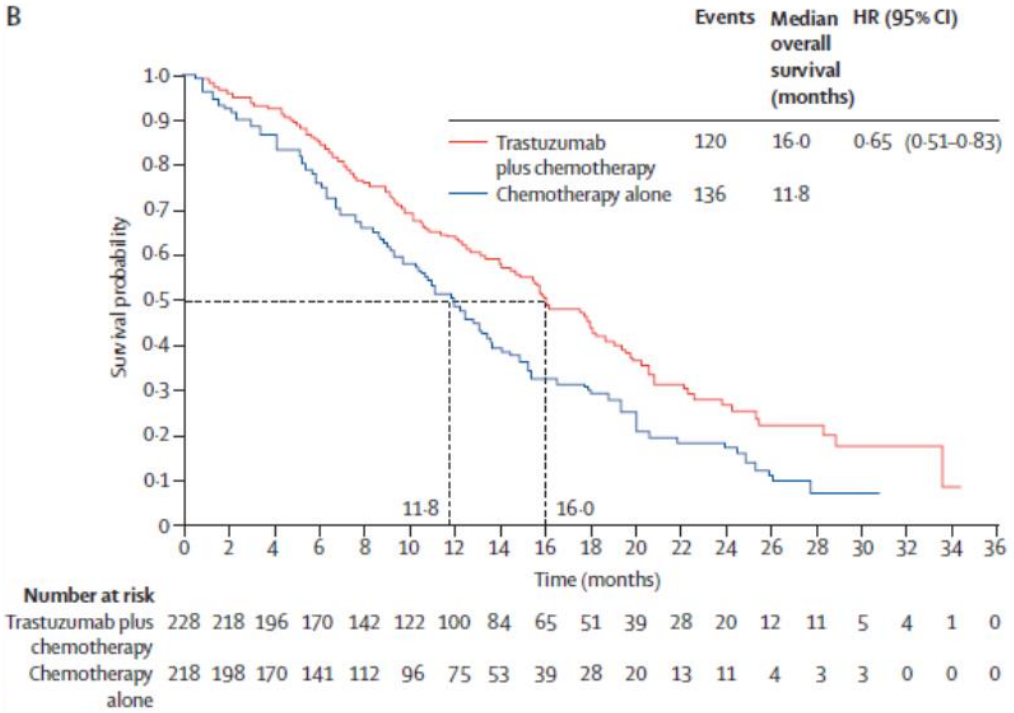
- 15-20% of gastroesophageal adenocarcinomas (GEA) are HER2+.
- HER2 testing is indicated for locally advanced and inoperable, recurrent, or metastatic tumors.
- No data to support targeting Her2 in early stage disease.
- In advanced disease, HER2 expression can change over time.
- Concurrent alterations in other signaling cascades and changes in HER2 expression changes can affect therapeutic options.

TOGA Trial: Trastuzumab in 1st LINE

TOGA Trial Design



HER2 IHC 3+ or IHC 2+/FISH+



Bang YJ, et al. Lancet. 2010;376:687-697

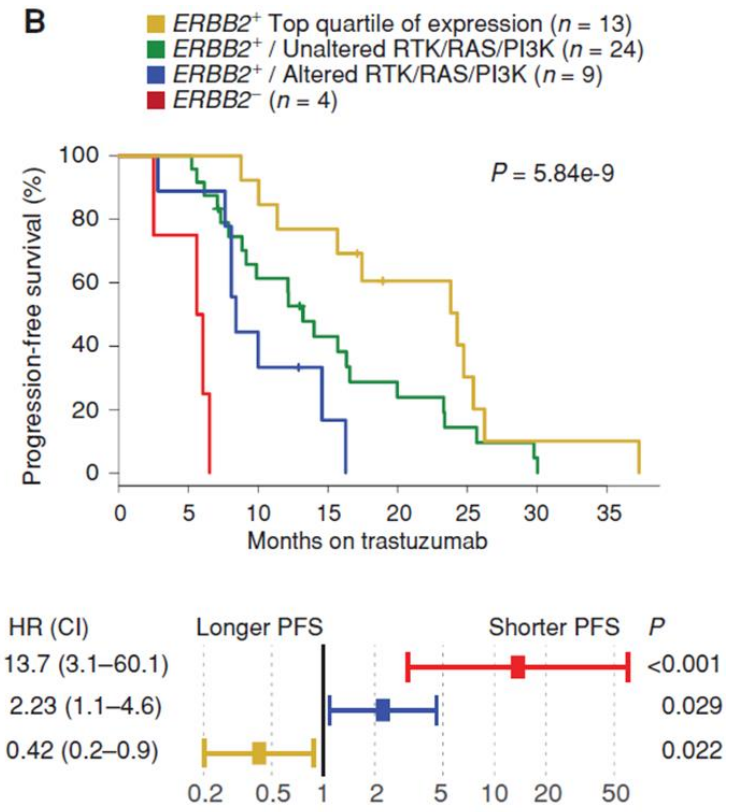
Other Attempts to Target Her2 in GEA

	Study	N	Treatment Arms	OS (mo)	HR p	
1st Line	TOGA[1]	584	5FU/cis 5FU/cis + Trastuzumab	11.1 13.8	HR 0.74 p < 0.001	✓
1st Line	LOGIC[2]	545	XELOX XELOX + Lapatinib	10.5 12.2	HR = 0.91 p = 0.34	⊘
1st Line	JACOB[3]	780	5FU/cis + trastuzumab 5FU/cis + trastuzumab + pertuzumab	14.2 17.5	HR = 0.84 p = 0.0565	⊘
2nd Line	TyTAN[4]	261	Paclitaxel Paclitaxel + lapatinib	8.9 11.0	HR = 0.54 p = 0.21	⊘
2nd Line	GATSBY[5]	415	T-DM1 Taxane	7.9 8.6	HR = 1.14 p =0.31	⊘
2nd Line	T-ACT[6] (Phase 2)	91	Paclitaxel Paclitaxel + Trastuzumab	9.95 10.20	HR = 1.23 p = 0.199	⊘

[1]Bang YJ, et al. Lancet. 2010;376:687-697, [2]Hecht et al, J Clin Oncol 2016 Feb 10;34(5):443-51; [3]Tabernero et al, Lancet Oncol. 2018 Oct;19(10):1372-1384; [4]Satoh et al, J Clin Oncol 2014 Jul 1;32(19):2039-49; [5]Thuss-Patience et al, Lancet Oncol. 2017 May;18(5):640-653; [6]Makiyama et a, J Clin Oncol. 2020 10;38(17):1919-1927

Tumor Heterogeneity And Evolution: A Challenge for Precision Oncology

Concurrent Genomic Alterations Influence Anti-HER2 Efficacy



Janjigian et al, Cancer Discovery 2018 (8): 49-58

Changes in Her2 Expression Over Time on Anti-Her2 Therapy

14/43 patients with loss of Her2 expression after trastuzumab

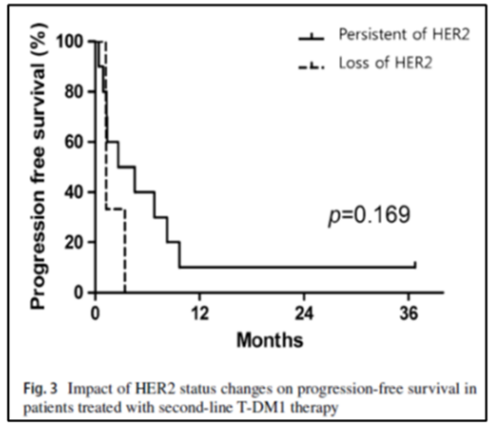
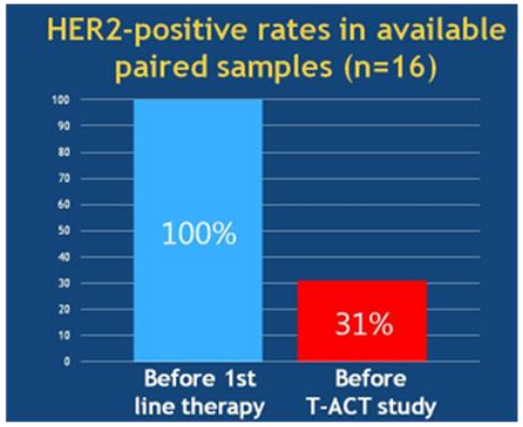
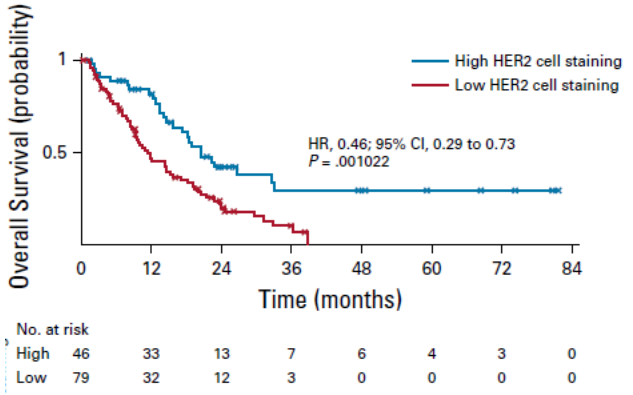


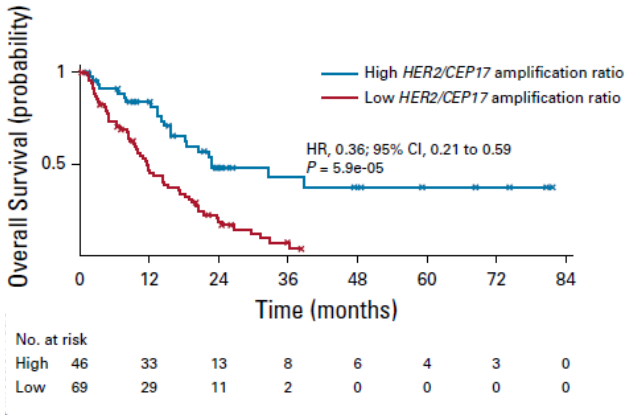
Fig. 3 Impact of HER2 status changes on progression-free survival in patients treated with second-line T-DM1 therapy



Sukawa et al, Abstr 4029, 2018 ASCO Meeting
Seo et al, Gastric Cancer 2019(22): 527-535

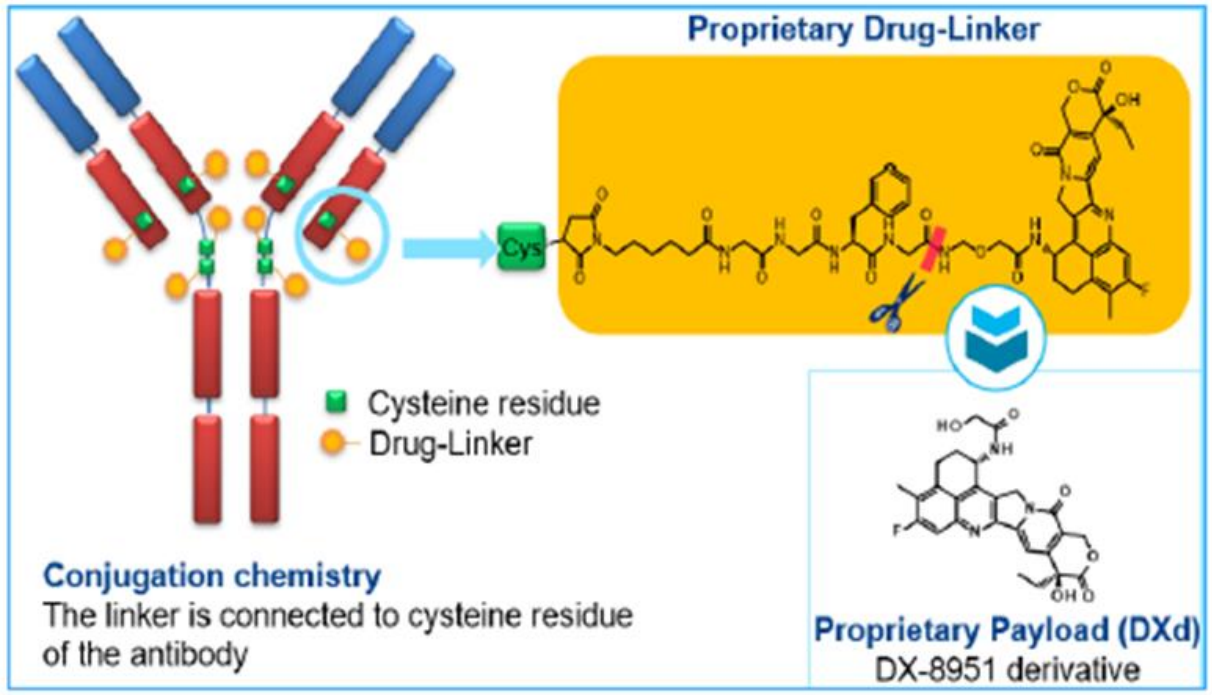
Level in Her2 Expression Over Time on Anti-Her2 Therapy





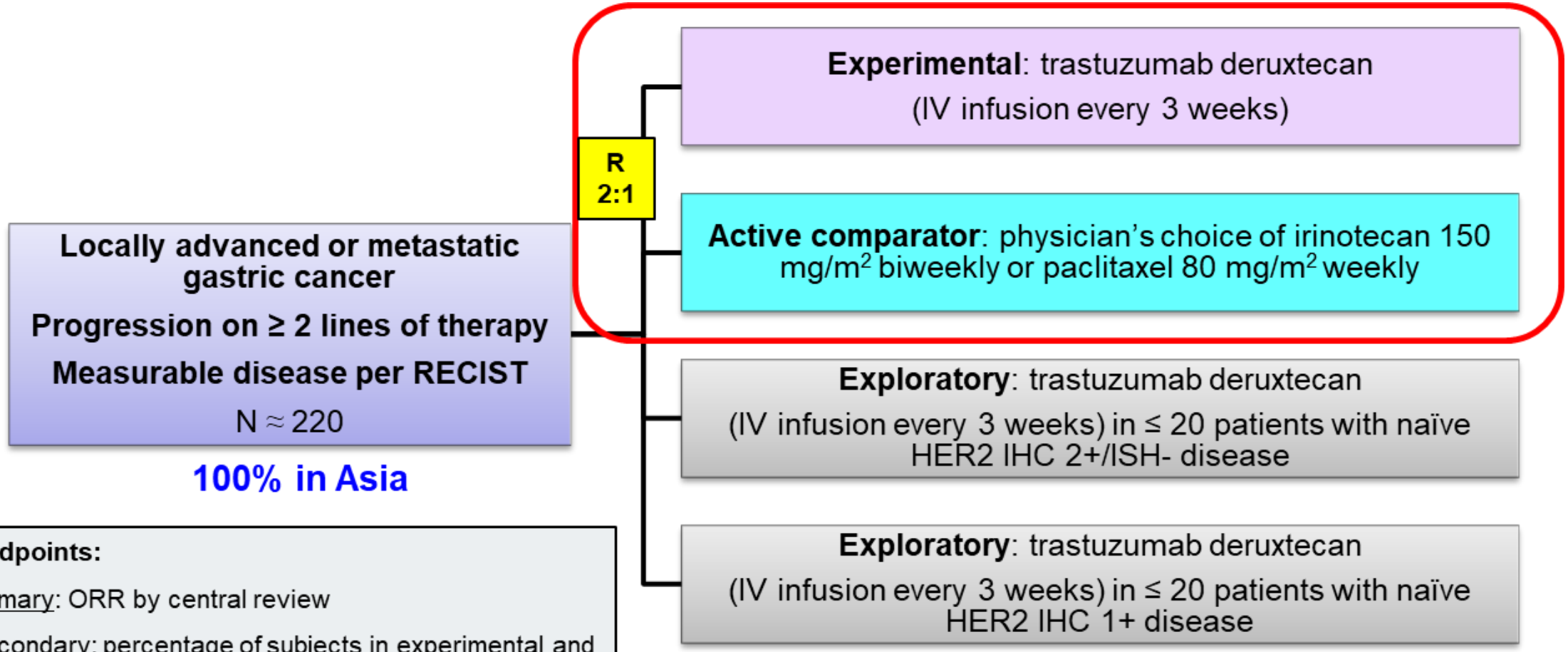
Haffner et al, JCO 2021(39): 1468-1478

Trastuzumab Deruxtecan: Mechanism of Action



- Humanized anti HER2 IgG1 mAb
- Topoisomerase I inhibitor payload
- High drug to antibody ratio: 7-8
- Payload with short systemic half-life
- Membrane permeable payload
- Tumor specific cleavable linker
- Bystander killing effect

DESTINY Gastric-01: Study Design



Endpoints:

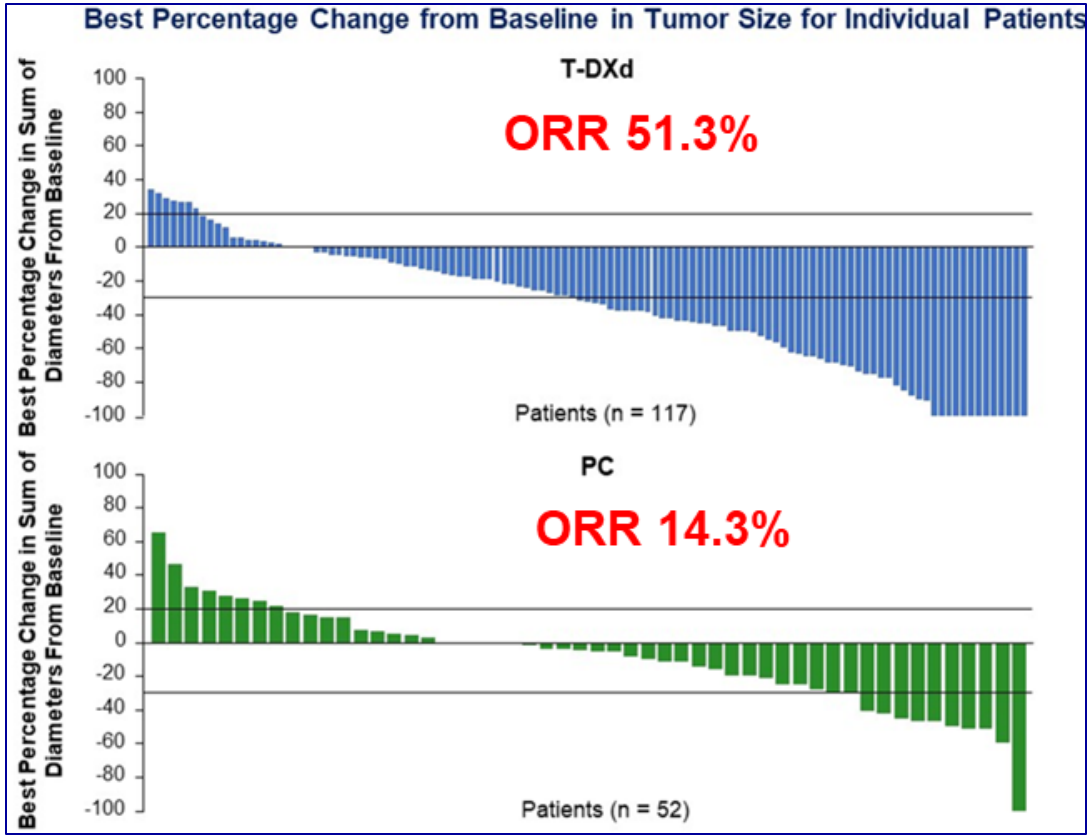
Primary: ORR by central review

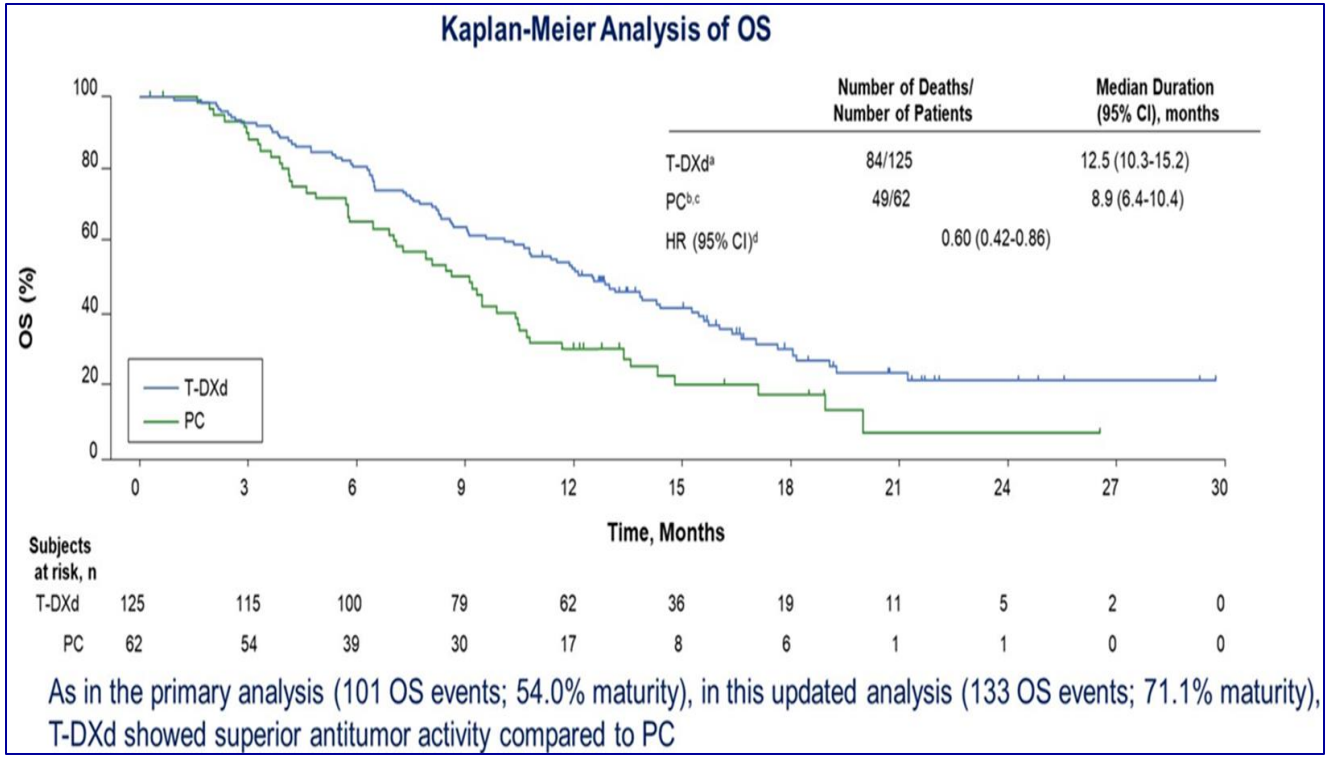
Secondary: percentage of subjects in experimental and active comparator groups with PFS, OS, DCR, TTFm C_{max}, AUC_{last}, AUC_{0-21}

Stratification: country, ECOG PS, HER2 status

Shitara et al, N Engl J Med 2020;382:2419-30

DESTINY-Gastric-01: Efficacy Results





Shitara et al, NEJM 2020 (382): 2419-2430

DESTINY-Gastric01: Safety Results

- Grade ≥3 AEs occurred in 85.6% of T-DXd patients versus 56.5% with PC
  - The most common were decreased neutrophil count (51.2% vs 24.2%), anemia (38.4% vs 22.6%), and decreased white blood cell count (20.8% vs 11.3%)
- 16 patients (12.8%) had T-DXd–related ILD/pneumonitis, as determined by an independent adjudication committee
  - There were 13 grade 1 or 2, 2 grade 3, 1 grade 4, and no grade 5 events
  - There were 4 ILD/pneumonitis events since the primary analysis; 1 grade 1 and 3 grade 2
  - Among the 16 total ILD/pneumonitis events, the median time to first onset was 102.5 days (range, 36-638)
  - There were no ILD/pneumonitis events in the PC arm
- There was 1 T-DXd-related death from pneumonia (non-ILD), as reported in the primary analysis
- There were no AE-related deaths in the PC arm

	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	21.6	7.2	0	24.2	3.2	0

AE, adverse event; ILD, interstitial lung disease; PC, physician's choice; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent AE.
No additional TEAEs were observed in ≥20% of patients receiving PC. [a]There were no grade 5 events. [b]Includes preferred terms "neutrophil count decreased" and "neutropenia." [c]Includes preferred terms "hemoglobin decreased," "red blood cell count decreased," "anemia," and "hematocrit decreased." [d]Includes preferred terms "platelet count decreased" and "thrombocytopenia." [e]Includes preferred terms "leukopenia" and "white blood cell count decreased." [f]Includes preferred terms "lymphocyte count decreased" and "lymphopenia."
Shitara K et al. *J Clin Oncol*. 2020;38:4513.

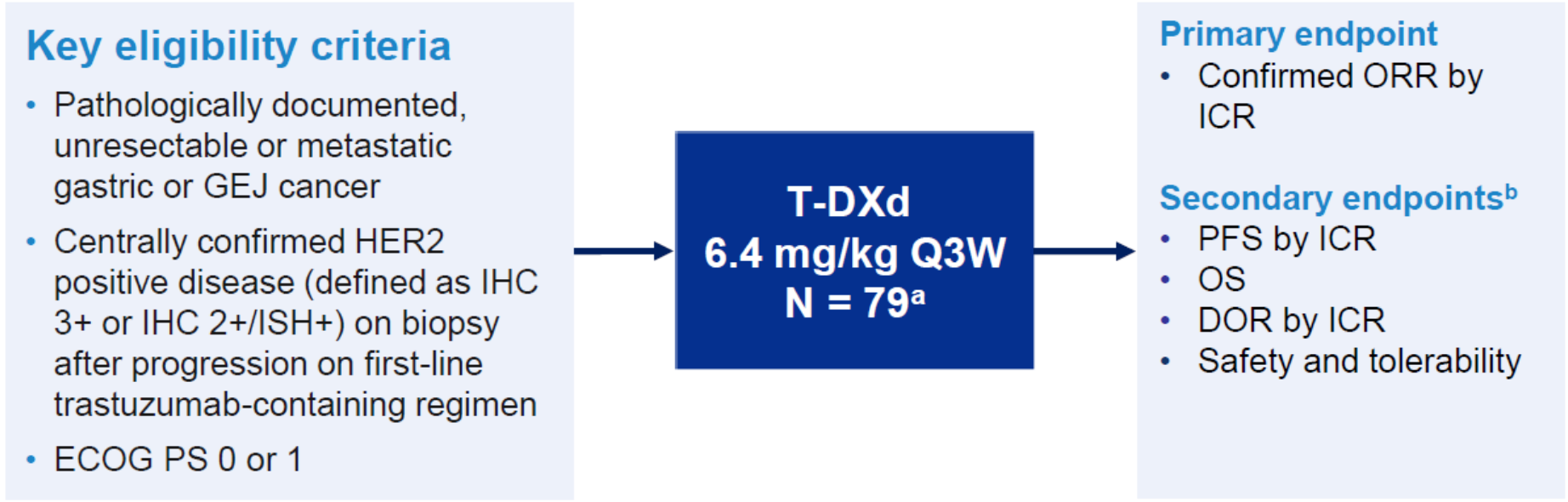
Presented at ASCO GI 2022 by Kensei Yamaguchi, MD

FDA Approval

1/15/2021: FDA approved fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo) for adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

Patient Selection for Locally Advanced or Metastatic Gastric Cancer Select patients with locally advanced or metastatic gastric cancer based on HER2 protein overexpression or HER2 gene amplification. ***Reassess HER2 status*** *if it is feasible to obtain a new tumor specimen after prior trastuzumab-based therapy and before treatment with ENHERTU.*

DESTINY-Gastric 02: Study Design

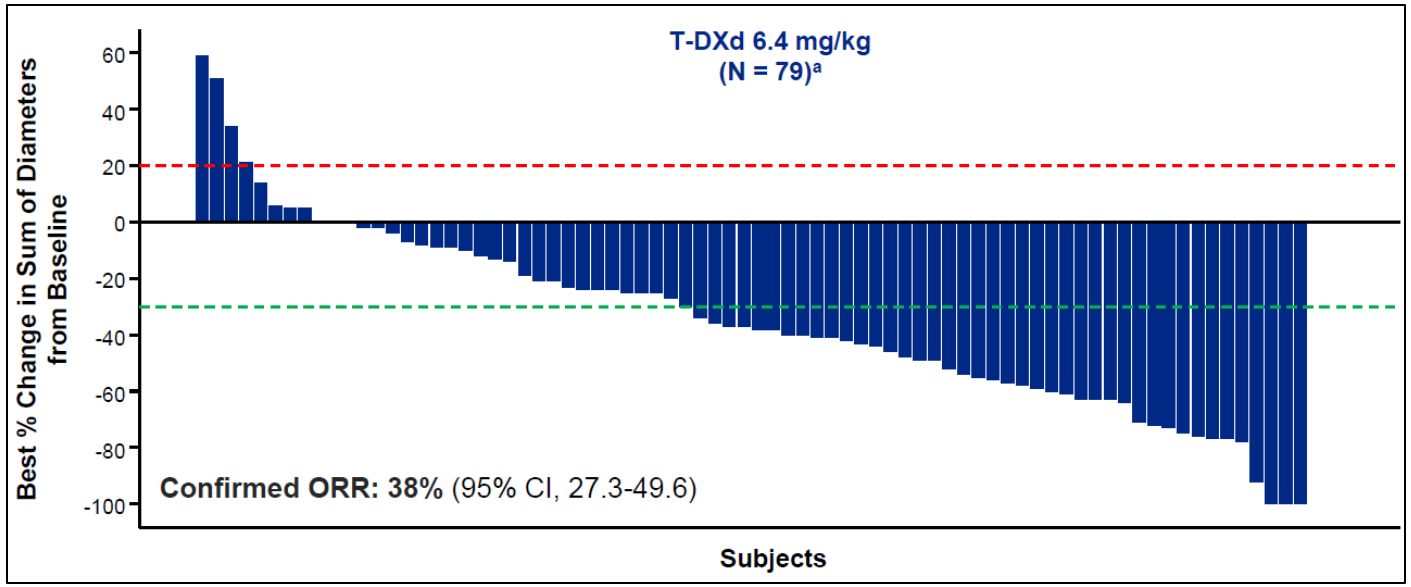


- DESTINY-Gastric02 is the first study focused only on second-line T-DXd monotherapy in Western patients with HER2+ gastric/GEJ cancer who have progressed on a trastuzumab-containing regimen
  - It is the follow-on study to DESTINY-Gastric01, which evaluated T-DXd third-line or later in Asian patients[1]
- Patients were enrolled in Europe (Belgium, Great Britain, Italy, Spain) and the United States (data cutoff: April 9, 2021)

2nd line study; Western patients
Her2 status confirmation after progression

Presented by Eric Van Cutsem, MD at ESMO 2021

DESTINY-Gastric 02: Efficacy and Safety Results



ORR 38%; DOR 8.1 months; DCR 81%; PFS 5.5 months

Drug-Related ILD/Pneumonitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
n (%)	2 (2.5)	3 (3.8)	0	0	1 (1.3)	6 (7.6)

- Median time to onset of adjudicated drug-related ILD/pneumonitis was 80.5 days (range, 53-85 days), with a median duration of 38.0 days (range, 15-142 days)
- 83% of adjudicated drug-related ILD/pneumonitis cases were low grade (Grade 1-2)

Presented by Eric Van Cutsem, MD at ESMO 2021

Ongoing Studies with T-DXd

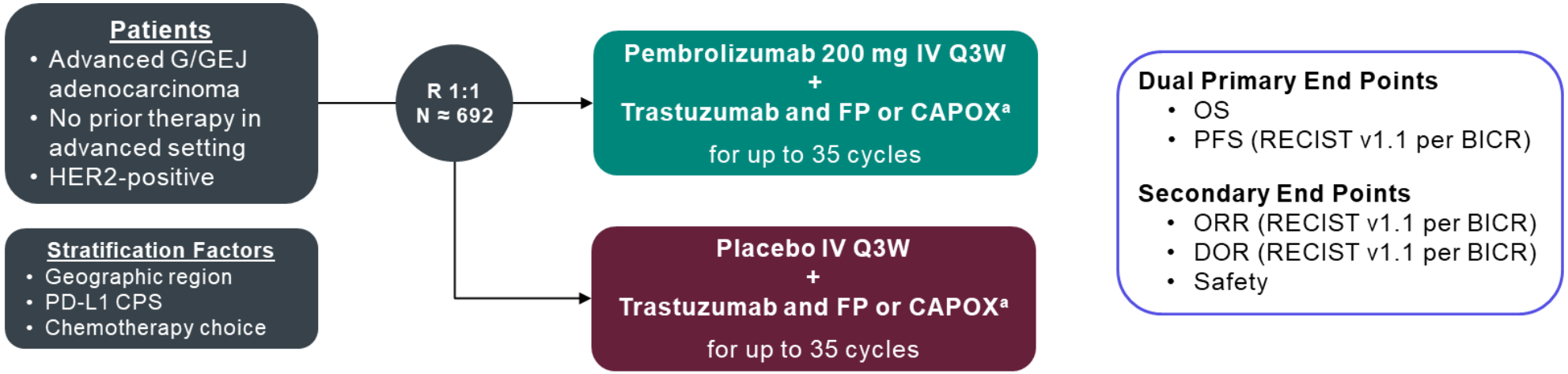
- **DESTINY-Gastric-04** (NCT04704934):

  Phase 3 Study of Trastuzumab Deruxtecan vs. Ramucirumab & Paclitaxel in patients With HER2+ Advanced G/GEJ adenocarcinoma that has progressed on 1 line of therapy.

- **DESTINY-Gastric-03** (NCT04379596):

  Phase 1/2 study of Trastuzumab Deruxtecan monotherapy and combinations (chemo, IO) in advanced HER2+ gastric cancer.

Immunotherapy for Her2+ GEA: Keynote 811



[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX dose: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100).

Protocol-Specified First Interim Analysis:

Timing: when the first **260** participants reach ≥8.5 months of follow-up

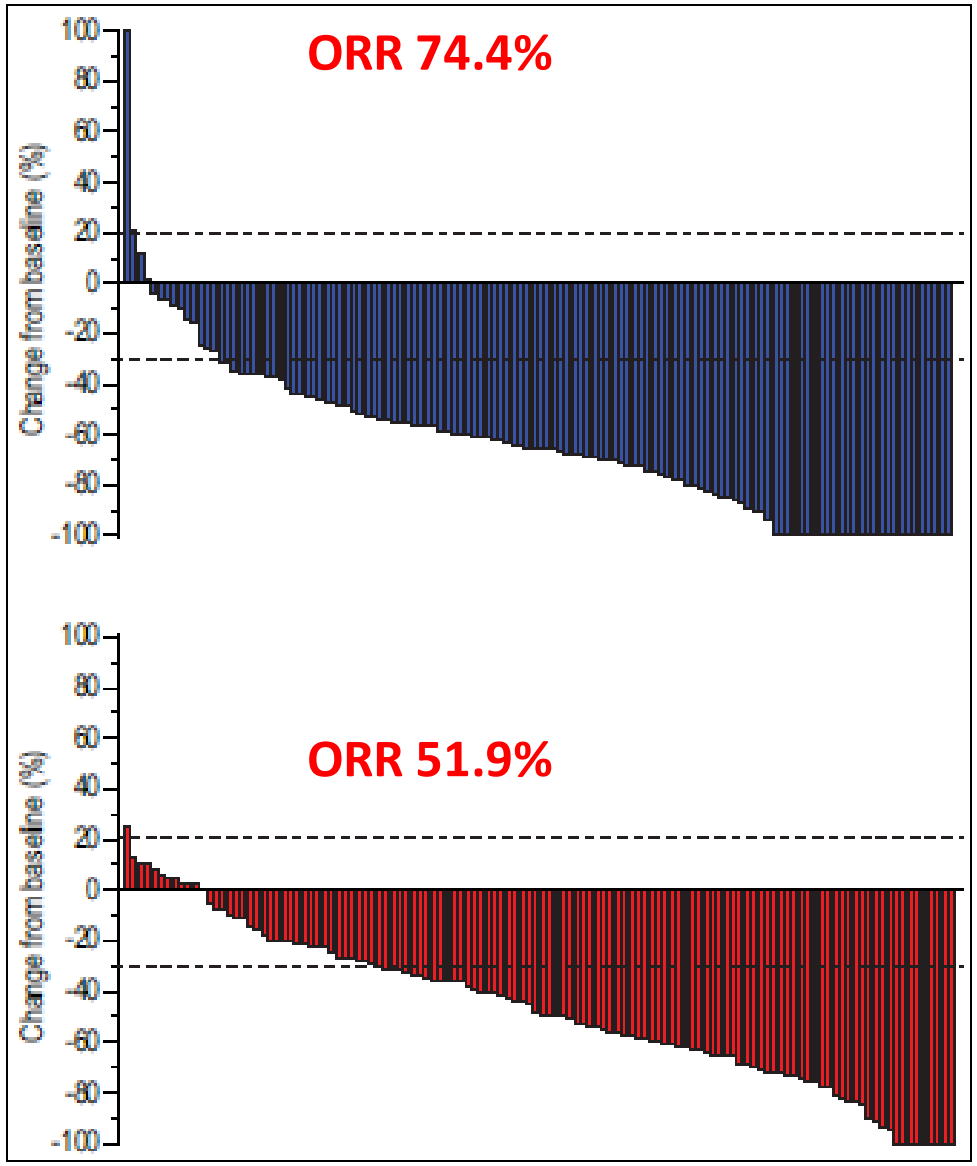
Objective: Evaluate overall response rate (ORR)

Superiority boundary: p=0.002 (one sided)

Data cut off 6/17/2020 (434 participants enrolled)

Presented by Janjigian et al, ASCO 2021

KEYNOTE 811: Interim Analysis Results



	Pembro (N=133)	Placebo (N=131)
ORR	74.4%	51.9% *p=0.00006*
CR	11 %	4%
DCR	96.2%	89.3%
DOR	10.6 mo	9.5 mo

ORR: objective response rate; CR: complete response; DCR: disease control rate; DOR: duration of response

5/5/2021: pembrolizumab received accelerated FDA approval in this setting

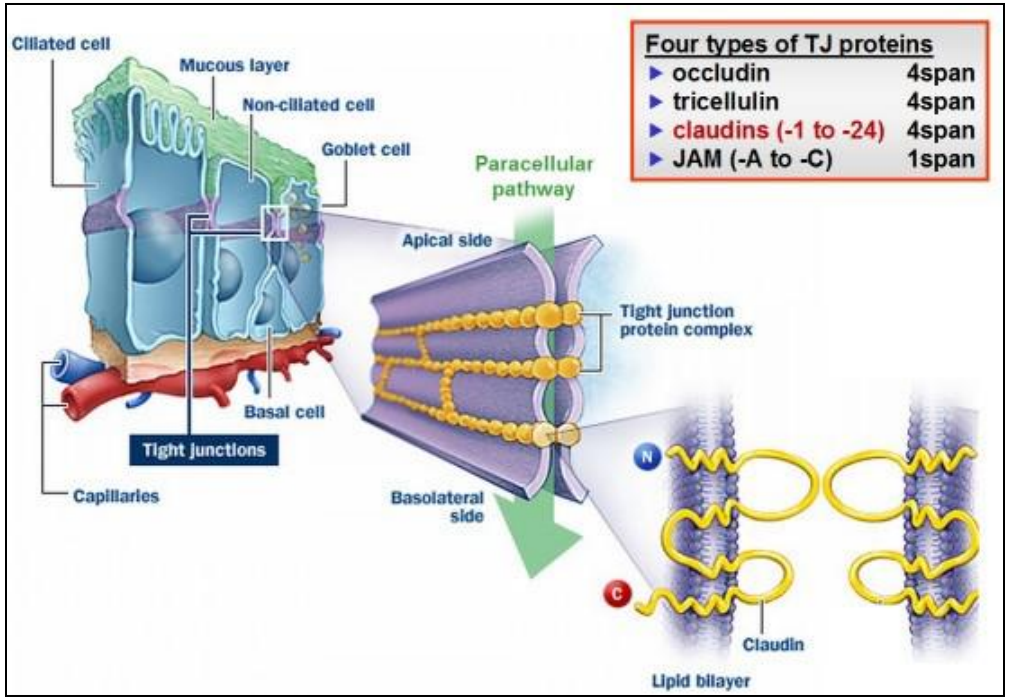
- Final analysis pending.
- Does PD-L1 expression matter?
- Benefit from IO beyond 1st line in Her2+ tumors?

Janjigian et al, Nature. 2021 Dec;600(7890):727-730

Outline

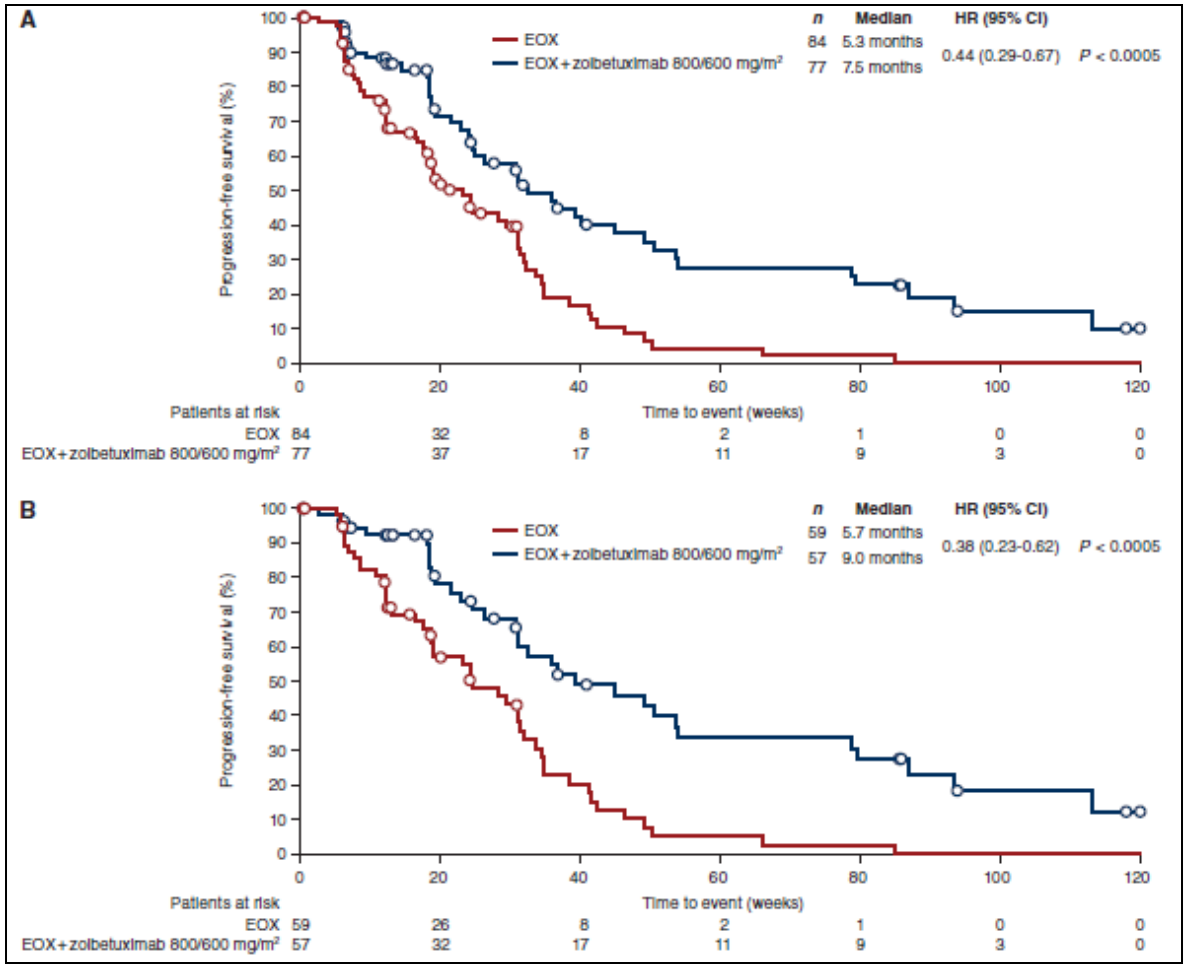
- Biomarker Testing
- Immunotherapy Use
  - Pivotal Phase 3 Studies in Advanced Disease
  - Early Stage Disease
  - MSI-High Tumors
- Targeting Her2 + GEA
- **Emerging Biomarkers**

Claudin 18.2



- Member of claudin family of proteins
- Component of tight junctions
- Expression in many cancers
- Not expression in healthy tissues, except for stomach mucosa

FAST: A randomised phase II study of **zolbetuximab (IMAB362)** plus EOX vs EOX alone for first-line treatment of advanced CLDN18.2 positive gastric and gastro-oesophageal adenocarcinoma



Sahin et al, Ann Oncol. 2021 May;32(5):609-619

FGFR2: Overexpression or Amplification

Key Eligibility Criteria

- No prior therapy for unresectable, locally advanced or metastatic gastric/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression and/or *FGFR2* gene amplification
- Not HER2-positive

Stratification Factors

- Geographic region
- Single dose of FOLFOX while screening
- Prior perioperative chemotherapy

Randomization 1:1

Bemarituzumab* + mFOLFOX6 (n = 77)

VS

Placebo + mFOLFOX6 (n = 78)

Primary endpoint
- PFS

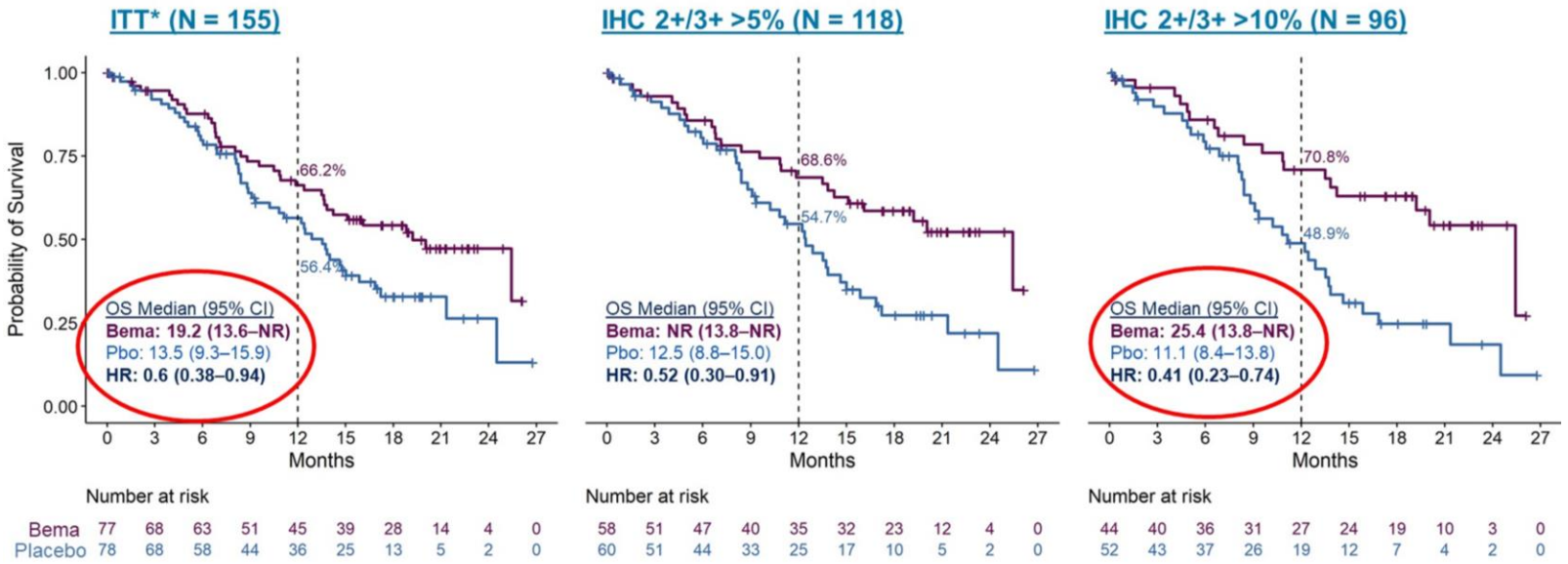
Secondary endpoints
- OS
- Response rate

Statistical Plan

Trial initially designed as registrational Phase 3 (n=548) with 2-sided α 0.05
Amended after enrolling n = 155 to a proof-of-concept Phase 2 with pre-specified statistical assumptions of:

- Hierarchical sequential testing: PFS, then OS/ORR
- ≥84 events to demonstrate benefit at a HR≤0.76 for PFS at 2-sided α of 0.2

Addition of Bemarituzumab Showed a +5.7 Month Improvement in Median OS



*ITT = includes 149 patients with IHC 2+/3+ and 6 with IHC <2+ or not available who were enrolled based on ctDNA alone.
NR, not reached.
Median Follow-up 12.5 months

*Based on February, 28th 2021 data cut

Presented by Catennacci et al, ASCO 2021

Summary and Future Directions

- PD-L1 CPS, MSI/dMMR, Her2 are established biomarkers in upper GI cancers.
- Treatment selection utilizing these biomarkers results in better efficacy.
- There are a number novel agents and biomarkers in development.
- Further validation is needed.
- Potential for biomarker overlap in the same tumor.
- We will need to learn how to prioritize, combine and sequence treatments based on efficacy and toxicity profiles.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