IMMUNOTHERAPY ACROSS ALL LINES OF TREATMENT IN UPPER GI CANCERS

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- No financial disclosures

Objectives

- Discuss biomarker driven treatment approach to esophagogastric cancers
- Discuss various trials that have led to approval of of immune check point inhibitors in upper GI cancers, esophageal, gastric and EGJ
- Discuss approach to MSI high upper GI cancers
- Future directions

Introduction

- Esophageal cancer causes more than half a million cancer-related deaths worldwide each year
- Most esophageal cancers are unresectable at diagnosis
- Most patients treated with curative intent eventually will relapse
- Standard fluoropyrimidine-plus-platinum–based chemotherapy for advanced or metastatic disease results in poor survival outcomes (median survival, <1 year)

- **The immunotherapy treatment landscape in gastric and esophageal cancer changed dramatically in the last 2 years**
- Since 2020, FDA has approved both nivolumab and pembrolizumab in combination with chemotherapy for patients with untreated advanced disease, and
- nivolumab has been approved by the FDA as adjuvant therapy for locoregional disease.
- Conversely, FDA approval for pembrolizumab in the third-line setting has been withdrawn

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY

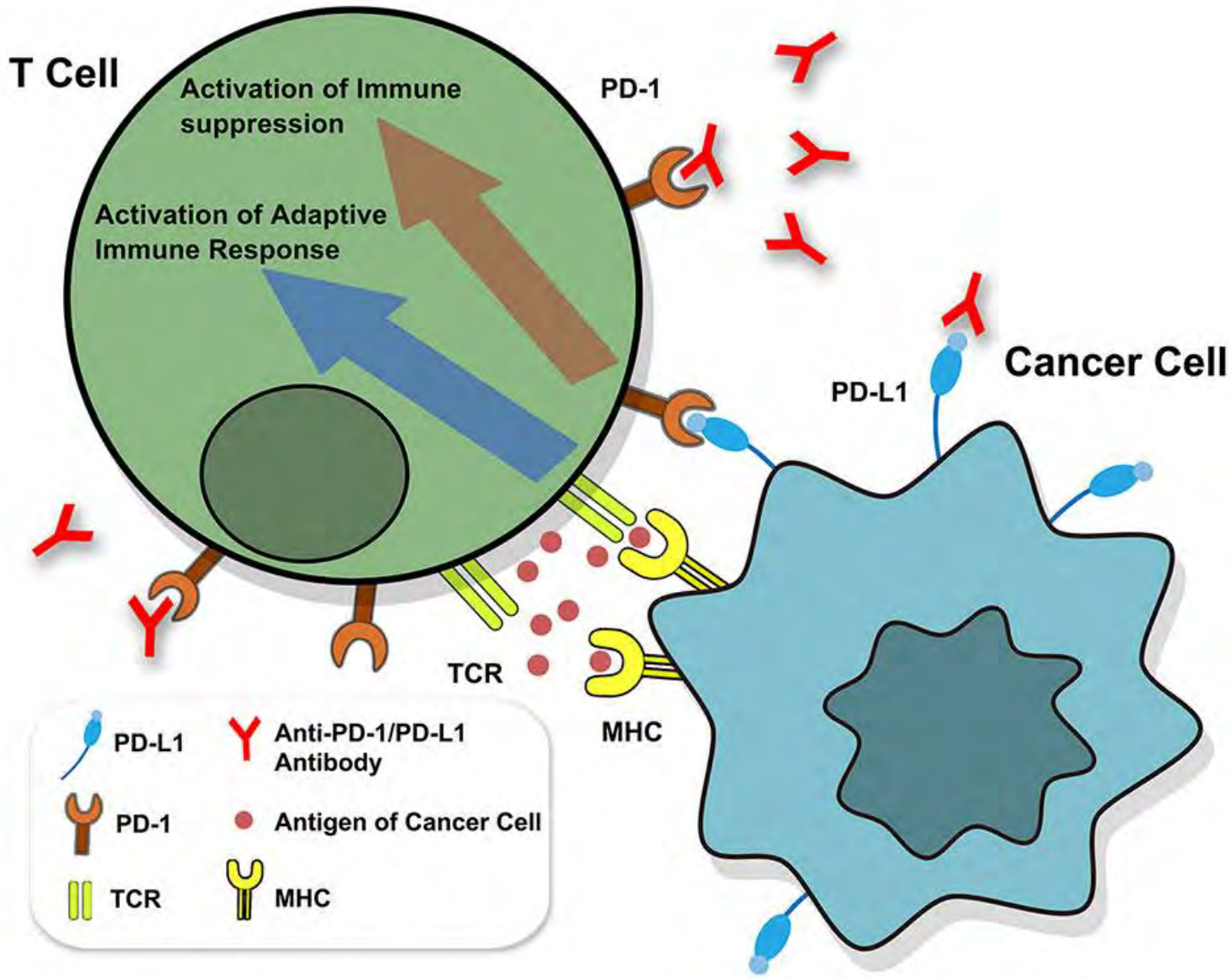
Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy

- **Oxaliplatin is generally preferred over cisplatin due to lower toxicity.**

Preferred Regimens

- **HER2 overexpression positive adenocarcinoma[g]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,18]**
- **HER2 overexpression negative[g]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab for adenocarcinoma (category 1 for PD-L1 CPS ≥ 5; category 2B for PD-L1 CPS <5)[e,h,19]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab for squamous cell carcinoma[e,h,20]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and nivolumab for squamous cell carcinoma[e,h,20]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (category 2A for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[e,h,21]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[e,h,21]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[22-24]**
  - **Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[22,25-27]**
  - **Nivolumab and ipilimumab for squamous cell carcinoma[e,h,20]**



Zhang et al. Frontiers in Pharmacology. 2020 May 15;11:722.

What are biomarkers for anti PD-1 therapy in gastric and esophageal cancer ?

- **PDL1** – standardization of PDL1 assessment is critical (preferred but imperfect) PD-L1 status does not guide therapy selection in early stage disease.
- Microsatellite instability (**MSI-H**) should be tested for all patients with GEJ cancers
- **TMB** - Tumor mutational burden - increase response rates, lacks significant prospective validation

Two accepted scoring systems

- **TPS** - percentage of tumor cells showing partial or complete staining relative to all tumor cells in the sample
- **CPS** - (CPS) is determined by the number of PDL1–staining cells, including tumor cells, lymphocytes, and macrophages, divided by the total number of viable tumor cells and multiplied by 100

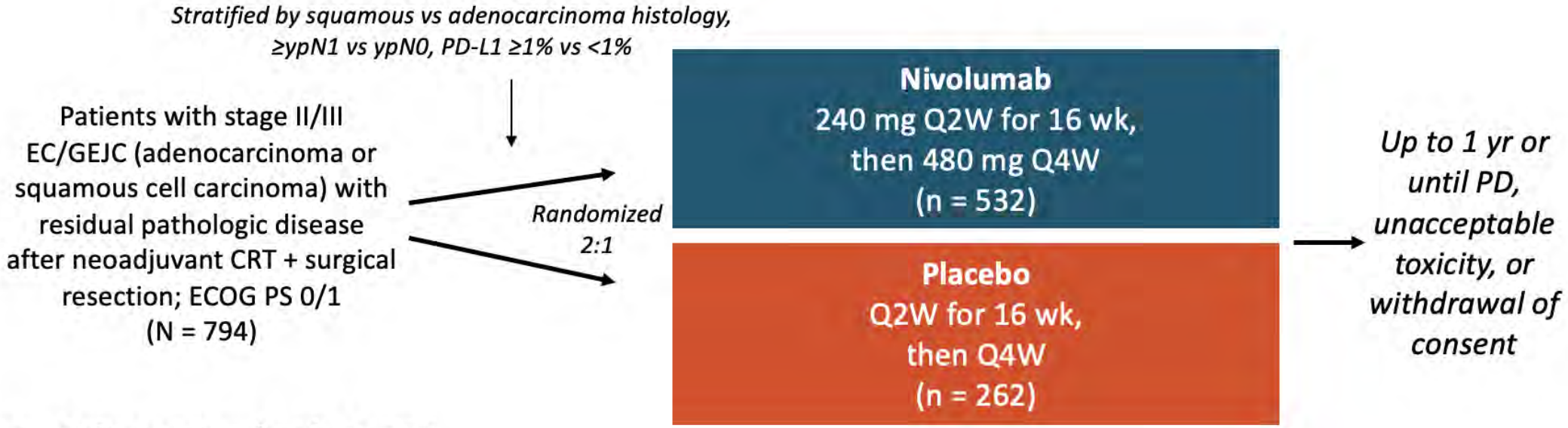
Immune checkpoint inhibitors in early stage Esophagus/EGJ cancer

Checkmate 577 trial – rationale

- High risk of recurrence after standard trimodality therapy for locally advanced EC/GEJC, especially those with residual disease
- No established adjuvant therapy in this setting

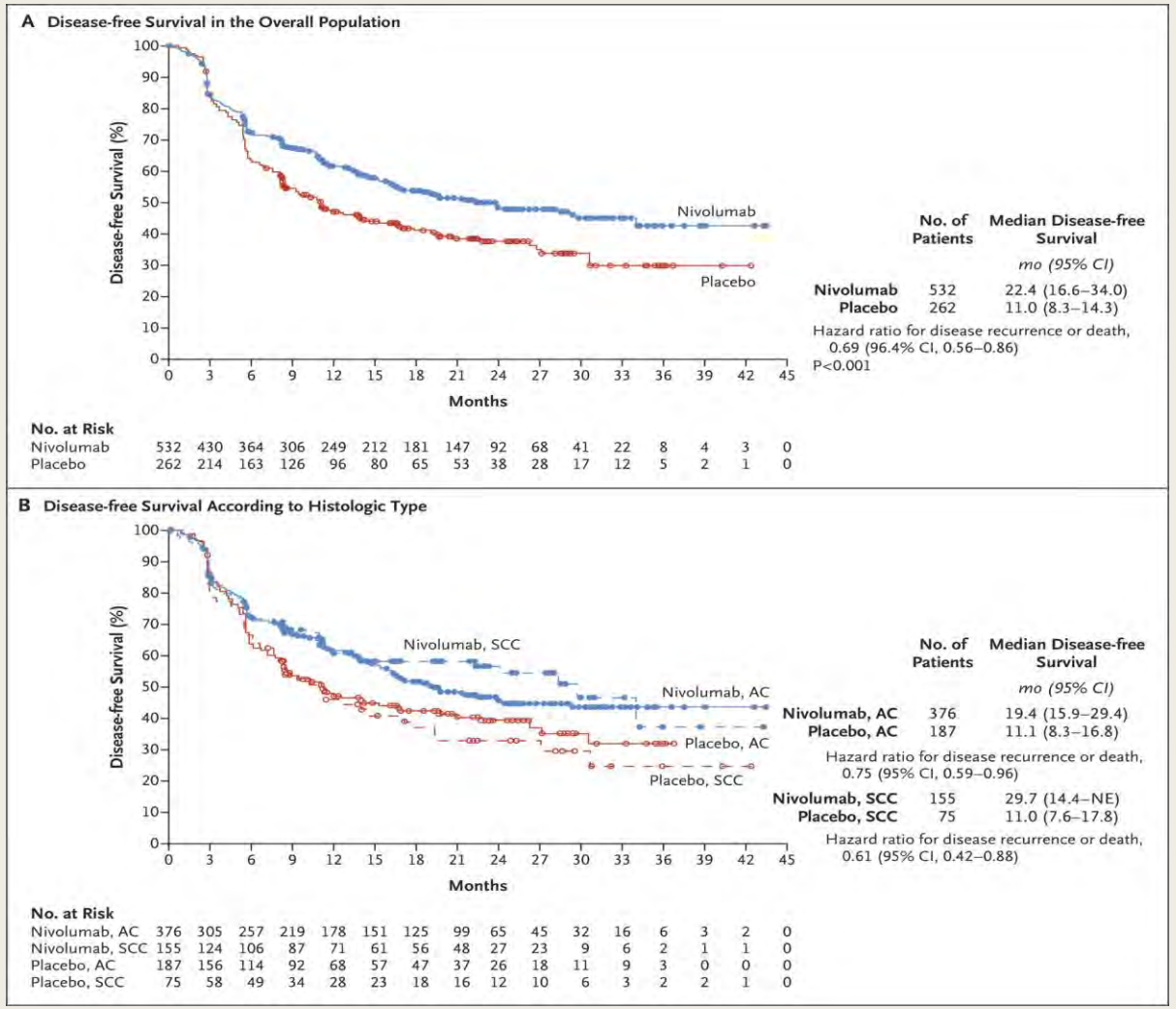
CheckMate 577 Update: Study Design

- Randomized, international, double-blind, placebo-controlled phase III study



- **Primary endpoint:** DFS
- **Secondary endpoints:** OS, OS rate at Yr 1, 2, and 3
- **Exploratory endpoints:** safety, DMFS, PFS2, QoL
- Median follow-up: 24.4 mo (range: 6.2-44.9)

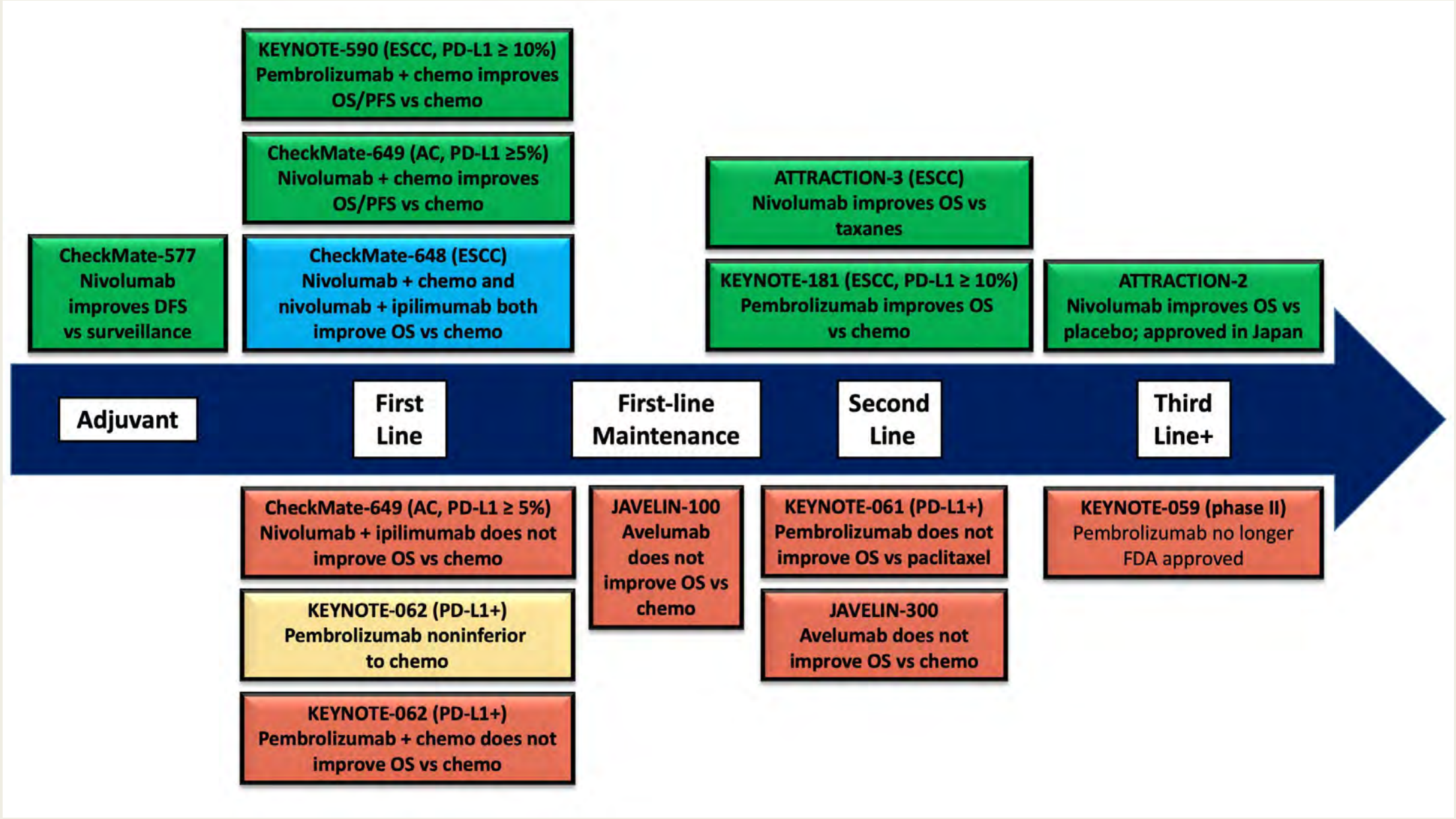
1. Kelly. NEJM. 2021;384:1191. 2. Kelly. ASCO 2021. Abstr 4003.



New England Journal of Medicine. 2021 Apr 1;384(13):1191-203.

Metastatic Esophago-gastric adenocarcinoma

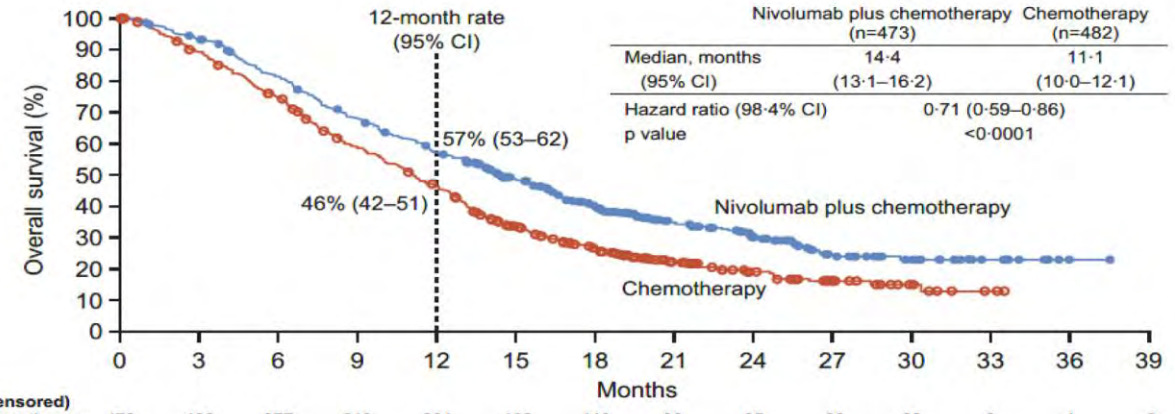
- First line setting – HER 2 negative disease


KEYNOTE-590 (ESCC, PD-L1 ≥ 10%) Pembrolizumab + chemo improves OS/PFS vs chemo
CheckMate-649 (AC, PD-L1 ≥5%) Nivolumab + chemo improves OS/PFS vs chemo
ATTRACTION-3 (ESCC) Nivolumab improves OS vs taxanes
CheckMate-577 Nivolumab improves DFS vs surveillance
CheckMate-648 (ESCC) Nivolumab + chemo and nivolumab + ipilimumab both improve OS vs chemo
KEYNOTE-181 (ESCC, PD-L1 ≥ 10%) Pembrolizumab improves OS vs chemo
ATTRACTION-2 Nivolumab improves OS vs placebo; approved in Japan
Adjuvant
First Line
First-line Maintenance
Second Line
Third Line+
CheckMate-649 (AC, PD-L1 ≥ 5%) Nivolumab + ipilimumab does not improve OS vs chemo
JAVELIN-100 Avelumab does not improve OS vs chemo
KEYNOTE-061 (PD-L1+) Pembrolizumab does not improve OS vs paclitaxel
KEYNOTE-059 (phase II) Pembrolizumab no longer FDA approved
KEYNOTE-062 (PD-L1+) Pembrolizumab noninferior to chemo
JAVELIN-300 Avelumab does not improve OS vs chemo
KEYNOTE-062 (PD-L1+) Pembrolizumab + chemo does not improve OS vs chemo

Study	Tumor Location and Histology	Geography	Biomarker Selection and Antibody Used	Study Design	OS, months	ORR	Grade ≥ 3 AEs	Grade ≥ 3 Immune-Mediated Events
First-line trials								
CheckMate 649	Esophageal/GEJ/gastric adenocarcinoma N = 1,581	17% United States and Canada 22% Asia 61% Rest of the world	PD-L1 CPS ≥ 5 PD-L1 CPS ≥ 1 All 28-8 pharmDx	Nivolumab plus chemotherapy[a] *v* chemotherapy	14.4 *v* 11.1 months in PD-L1 CPS ≥ 5, HR 0.71, $P < .0001$ 14.0 *v* 11.3 months in PD-L1 CPS ≥ 1, HR 0.77, $P = .0001$ 13.8 *v* 11.6 months in all, HR 0.80, $P = .0002$	60% *v* 45% PD-L1 CPS ≥ 5 60% *v* 46% in PD-L1 CPS ≥ 1 58% *v* 46% in all	59% *v* 44% (all patients)	15% *v* 6%
CheckMate 648	ESCC N = 970	70% Asia 30% Non-Asia	PD-L1 TPS ≥ 1 28-8 pharmDx	Nivolumab plus chemotherapy[b] Nivolumab and ipilimumab Chemotherapy	15.4 months in PD-L1 TPS ≥ 1; HR 0.54, $P < .001$ 13.2 months in all, HR 0.74, $P = .002$ 13.7 months in PD-L1 TPS ≥ 1, HR 0.64, $P = .001$ 12.7 months in all, HR 0.78, $P = .01$ 9.1 months in TPS ≥ 1 10.7 months in all	53% in PD-L1 TPS ≥ 1; 47% in all 35% in PD-L1 TPS ≥ 1; 28% in all 20% in PD-L1 TPS ≥ 1; 27% in all	47% 32% 36%	9% 19% 5%
ATTRACTION-4	Gastric/GEJ adenocarcinoma N = 724	Japan, Korea, Taiwan	None 28-8 pharmDx	Nivolumab plus chemotherapy[c] *v* chemotherapy	17.45 *v* 17.15 months, HR 0.90, $P = .26$	57.5% *v* 47.8%	57% *v* 48%	17% *v* 0

Patel et al. Journal of Clinical Oncology. 2022 Aug 20;40(24):2751-62.

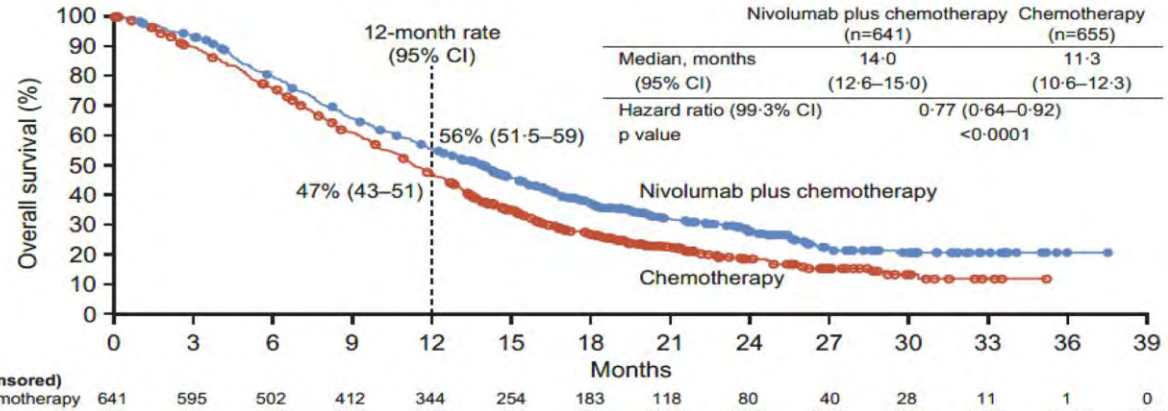
A PD-L1 CPS ≥5



	Nivolumab plus chemotherapy (n=473)	Chemotherapy (n=482)
Median, months (95% CI)	14·4 (13·1–16·2)	11·1 (10·0–12·1)
Hazard ratio (98·4% CI)	0·71 (0·59–0·86)	
p value	<0·0001	

Number at risk (censored)														
Nivolumab plus chemotherapy	473	438	377	313	261	198	149	96	65	33	22	9	1	0
	(0)	(3)	(9)	(11)	(14)	(39)	(55)	(91)	(110)	(133)	(142)	(155)	(163)	(164)
Chemotherapy	482	421	350	271	211	138	98	56	34	19	8	2	0	0
	(0)	(10)	(13)	(19)	(21)	(37)	(50)	(78)	(93)	(103)	(113)	(118)	(120)	(120)

B PD-L1 CPS ≥1



	Nivolumab plus chemotherapy (n=641)	Chemotherapy (n=655)
Median, months (95% CI)	14·0 (12·6–15·0)	11·3 (10·6–12·3)
Hazard ratio (99·3% CI)	0·77 (0·64–0·92)	
p value	<0·0001	

Number at risk (censored)														
Nivolumab plus chemotherapy	641	595	502	412	344	254	183	118	80	40	28	11	1	0
	(0)	(3)	(11)	(13)	(17)	(51)	(76)	(118)	(142)	(169)	(179)	(196)	(206)	(207)
Chemotherapy	655	575	483	383	292	194	131	77	45	25	10	3	0	0
	(0)	(14)	(17)	(24)	(27)	(54)	(74)	(108)	(128)	(141)	(154)	(160)	(163)	(163)

Janjigian et al.The Lancet. 2021 Jul 3;398(10294):27-40.

First-Line Setting: HER2-Positive disease

- About 20% of EGA overexpress HER2 or harbor HER2 gene amplification.
- Trastuzumab in combination with chemotherapy has been the standard first-line treatment for these tumors for over a decade.
- Keynote 811 trial, evaluating addition of pembrolizumab
- At the preplanned interim analysis of KEYNOTE-811 after enrollment of 260 participants with at least 8.5 months of follow-up, pembrolizumab significantly increased ORR compared with placebo (74.4% v 51.9%)
- There were no new safety signals, and the addition of pembrolizumab to standard therapy is now FDA-approved and endorsed by the NCCN guidelines in this setting, regardless of tumor PD-L1 status

Janjigian et al Nature 600:727-730, 2021.

Second-Line and Beyond

- Studies enrolled IO-naive patients, and thus the results have become largely irrelevant at a time when anti–PD-1 antibodies are FDA-approved in first-line and adjuvant settings

MSI high upper GI cancers

- About 4%-22% of gastroesophageal tumors are mismatch repair deficient (dMMR)/MSI-H, which is associated with improved clinical prognosis
- In resectable/early stage disease - MSI-H gastric and GEJ tumors may derive no benefit from perioperative chemotherapy
- In the exploratory analysis of patients with MSI-H tumors enrolled in the perioperative MAGIC trial, MSI-H tumors had a better prognosis when treated with surgery
- The prospective phase II GERCORNEONIPIGA study that enrolled 32 patients with MSI-H gastric and GEJ cancers demonstrated an unprecedented pathologic complete response rate of 59% with preoperative nivolumab and ipilimumab

Smyth et al. JAMA Oncol 3:1197-1203, 2017,
Andre et al. J Clin Oncol 40, 2022 (abstr 244)

Future directions

- An ongoing phase II/III EA2174 study is evaluating whether the addition of nivolumab to chemoradiation in the preoperative setting and ipilimumab to adjuvant nivolumab can improve upon efficacy seen in checkmate 577
- KEYNOTE 585 is a global phase III trial evaluating the benefit of pembrolizumab with perioperative FLOT (fluorouracil, leucovorin, oxaliplatin, docetaxel) chemotherapy (ClinicalTrials.gov identifier: NCT03221426)
- The MATTERHORN trial is a phase III study of perioperative durvalumab with FLOT chemotherapy (ClinicalTrials.gov identifier: NCT04592913)
- Emerging immune targets, such as TIGIT and DKK1, are being evaluated in ongoing trials after promising activity in earlier studies

Summary

- Is chemo-imumotherapy the new standard of care for first line treatment of metastatic disease ?
- YES – CPS >5 (for GE adenocarcinomas)
- YES – for ESCC CPS >10
- Detatable for the other subgroups
- Going forward, a uniform and simplified approach to PD-L1 testing is much needed
- Need for continued optimization of PD-L1 as a biomarker and for identification of new predictive biomarkers.
- Need more data to support use of ICI in the MSI high setting
- Significant unmet need to improve outcomes in patients with PD-L1–negative tumors across therapy lines